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ORIGINAL ARTICLE

Changes in the rate of and trends in colectomy for ulcerative colitis during the era of biologics and calcineurin inhibitors based on a Japanese nationwide cohort study

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Abstract

Purpose We evaluated the recent incidence of surgery and the changing surgery trends for ulcerative colitis (UC) in Japan due to the increasing use of anti-tumor necrosis factor (TNF) agents.

Methods A questionnaire survey was performed to assess the number of surgeries, surgical indications, surgical timing, and immunosuppressive treatments before surgery between 2007 and 2017.

Results A total of 3801 surgical cases were reported over 11 years. The prevalence of UC surgery decreased over the period studied. The rate of prednisolone (PSL) use did not change. The prevalence of both calcineurin inhibitors (CNIs) and anti-TNF agents increased during the period studied ($p < 0.01$). The prevalence of urgent/emergent surgery did not change. The most distinctive change in surgical indications was the increase in cancer/dysplasia (CAC), the prevalence of which increased from 20.2% in 2007 to 34.8%.

Conclusion The prevalence of UC surgery seems to be decreasing according to the increasing rate of anti-TNF agent and CNI administration. However, the indication of CAC significantly increased. Further research should evaluate whether or not long-term remission maintained with several agents can lead to increasing CAC.

Keywords Ulcerative colitis · Colectomy · Anti-tumor necrosis factor alpha · Calcineurin inhibitor

Introduction

Recently, the prevalence of ulcerative colitis (UC) has been increasing worldwide [1, 2]. However, the rate of colectomy has declined as the use of anti-tumor necrosis factor (TNF) agents has increased according to a 2010 report from Sweden [2] and 2011 and 2014 reports from Canada [3, 4]. Moore et al. reported that the risk of colectomy decreased from 10% in the pre-infliximab (IFX) era to 8.9% in the post-IFX era [4]. Sandborn et al. reported that compared to placebo use, the use of IFX could reduce the risk of colectomy in UC by 41% during 54 weeks of administration [5]. The cumulative risk of colectomy 10 years after the diagnosis was estimated to be 28% in a report from Sweden before 2000 [6]. However, that incidence was reported to be 7.6% after 10 years in a Chinese report from 2009 [7].

Calcineurin inhibitors (CNIs), which include tacrolimus and cyclosporine, are known to be effective for the rescue of severe UC, although a high relapse rate for colectomy was reported [8–10].

Although some contributions of novel therapies have reduced the need for colectomy in patients with refractory disease, colitis-associated cancer/dysplasia (CAC) may be increasing as the duration of disease increases. Therefore, the overall natural history of UC remains unclear. In addition, the incidence and prevalence of UC and its colectomy rate may differ widely across geographical regions.

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In the present study, we evaluated the incidence of surgery and recent changes in surgical trends for UC in Japan during the era of anti-TNF agents and CNIs.

Methods

Questionnaires about surgical trends were sent to the 25 leading institutions in Japan specializing in and having experience with inflammatory bowel disease (IBD) surgery. The questions assessed the number of UC surgeries and their surgical indications; surgical timing, which included elective or urgent/emergent; and immunosuppressive agents used before surgery every year between 2000 and 2017. The total number of surgeries was collected and analyzed. However, there were no data before 2007 in some institutions, so the trend in the number of surgeries was analyzed between 2007 and 2017. In addition to immunosuppressive therapies, the prevalence of prednisolone (PSL), CNI, and anti-TNF agent usage was also collected.

The surgical indications consisted of refractory UC, perforation, toxic megacolon, extraintestinal manifestation, and CAC. Urgent/emergent surgery was defined as all unplanned surgery that included surgery for severe or fulminant UC unresponsive to several immunosuppressive therapies, perforation, or toxic megacolon. Emergent surgery was defined and restricted to surgery for perforation and toxic megacolon. The use history of all immunosuppressive agents before surgery was collected regardless of their timing before surgery to determine and evaluate the historical trends for each agent.

The total administered PSL dose was calculated based on the previously administered steroid dose, which was converted to PSL after the initial diagnosis. The dose trend analyses for total PSL and preoperative PSL administered were reviewed and analyzed based on historical data from Hyogo College of Medicine.

Ethical considerations

All study protocols were approved by the institutional review board at Hyogo College of Medicine with approval No. 3145.

Statistical analyses

A trend analysis was performed by a forecast analysis of the number of surgeries divided by the total number of UC patients in Japan in each year with a 95% confidence interval. The total UC incidence in Japan in each year was collected in a nationwide effort by the Ministry of Health, Labour and Welfare in Japan that examined the nationwide prevalence of UC every year [11, 12]. The prevalence of immunosuppressive agents was analyzed by an analysis of variance (ANOVA). The changes in the PSL dose were analyzed by a non-repeated measures ANOVA. Data organization and analyses and graph creation were performed using the software programs Microsoft® Excel® 2016 (Microsoft Corporation: One Microsoft Way, Redmond, WA, USA) and SPSS ver. 15.0 (SPSS Inc., Tokyo, Japan). The level of statistical significance was set at $p < 0.05$.

Results

We obtained responses and collected questionnaires from 20/25 (80%) institutions. A total of 3801 surgical cases over 11 years were reported. Restorative proctocolectomy (RPC), which is confirmed by insurance, is performed only for patients with UC and familial adenomatous polyposis coli (FAP) in Japan. The National Clinical Database (NCD), which collects several surgical procedures as a nationwide surgical database and began keeping records in January 2011, contains records of ≥ 95% of the surgeries carried out by regular surgeons in Japan [13]. The NCD reports the number of RPCs in Japan annually, as indicated in Table 1 [14]. The number of surgeries in our survey accounted for 70–100% of NCD records.

Surgical trends in Japan

The prevalence of surgery calculated by the number of surgeries/registered number of individuals diagnosed with UC in Japan is indicated in Fig. 1. The historically registered number of Japanese UC patients can be found in a previous report and on the website of the Japan Intractable Diseases Information Center [12, 15]. The prevalence of UC surgery

Table 1 Number of surgical cases in each year

	2007	2008	2009	2010	2011	2012	2013	**2014**	**2015**	**2016**	**2017**
(1) Number of RPC in questionnaire	362	334	334	323	308	369	361	326	363	382	339
(2) Number of RPC in NCD report	–	–	–	–	308	413	441	468	499	479	-
Ratio (1)/(2)	–	–	–	–	100%	89%	82%	70%	73%	80%	-

RPC restorative proctocolectomy, *NCD* National Clinical Database

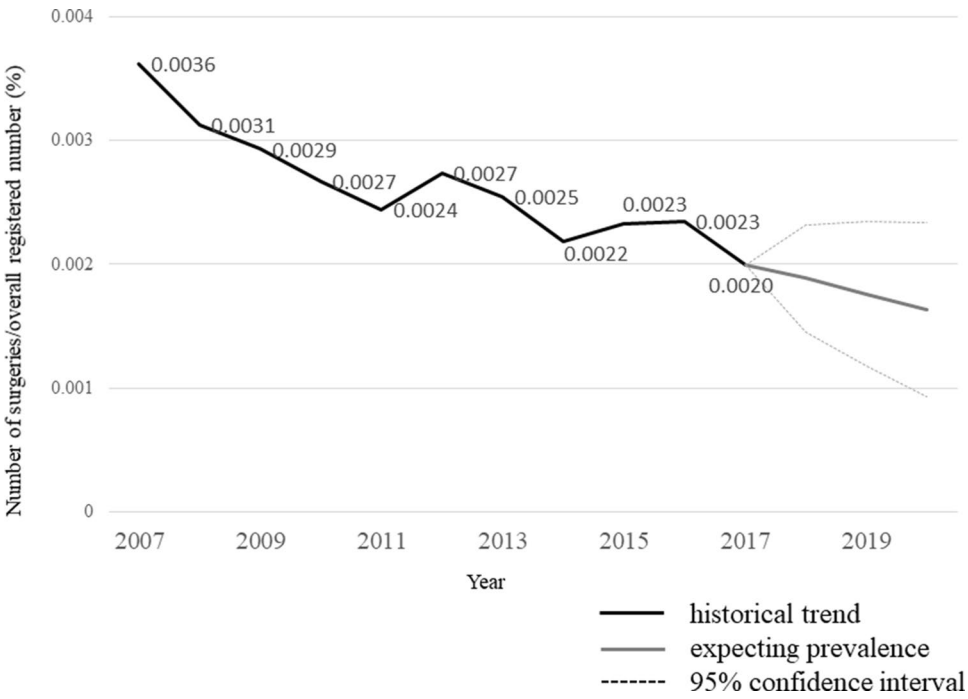

Fig. 1 Historical prevalence of surgical cases among all patients with ulcerative colitis in Japan. The historical prevalence and expected prevalence both show decreasing trends

seems to decrease across the study period and is expected to continue decreasing in the future, although the absolute number of surgeries each year was similar and ranged between 308 and 382 a year ($p = 0.99$).

Patient background characteristics and immunosuppressive agents administered before surgery

The historical changes in the administration of PSL before surgery are indicated in Fig. 2. The rate of a history of PSL use did not change over time. Although the historical changes in patient background characteristics and PSL dose were not included in this questionnaire, the total PSL

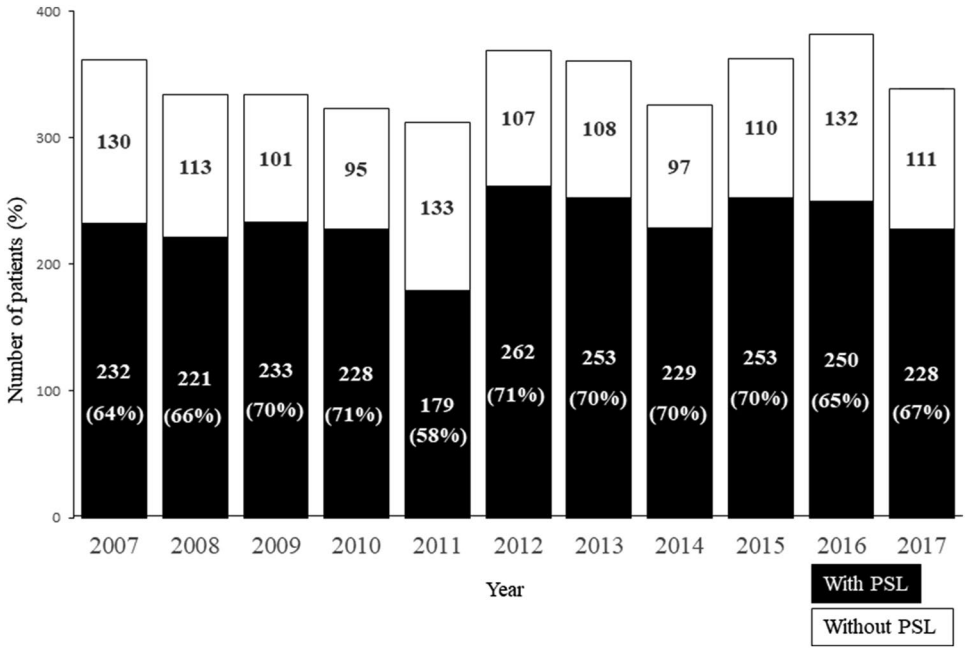

Fig. 2 The incidence of prednisolone (PSL) administration before surgery in surgical patients. The percentage is shown in parentheses. PSL administration showed no marked historical change ($p = 0.57$)

dose given before surgery and the preoperative daily PSL dose both significantly decreased over the study period at Hyogo College of Medicine. At this institution, the age at the onset (mean ± standard deviation [SD]) significantly increased from 31.7 ± 12.8 years among 101 patients in 2007 to 43.0 ± 19.8 years among 81 patients in 2017 ($p < 0.01$), while the disease duration did not change markedly (9.8 ± 8.1 years in 2007 to 10.1 ± 9.8 years, $p = 0.85$). The total PSL dose and preoperative daily PSL dose (mean ± SD) given in 2007 were 13,419 ± 14,555 mg and 22.2 ± 22.6 mg, respectively; these values significantly decreased to 7248 ± 13,930 mg and 7.6 ± 14.4 mg, respectively, in 2017 ($p < 0.01$), although the disease durations were similar.

The prevalence of CNI and anti-TNF agent use both increased during the study period (Fig. 3a, b).

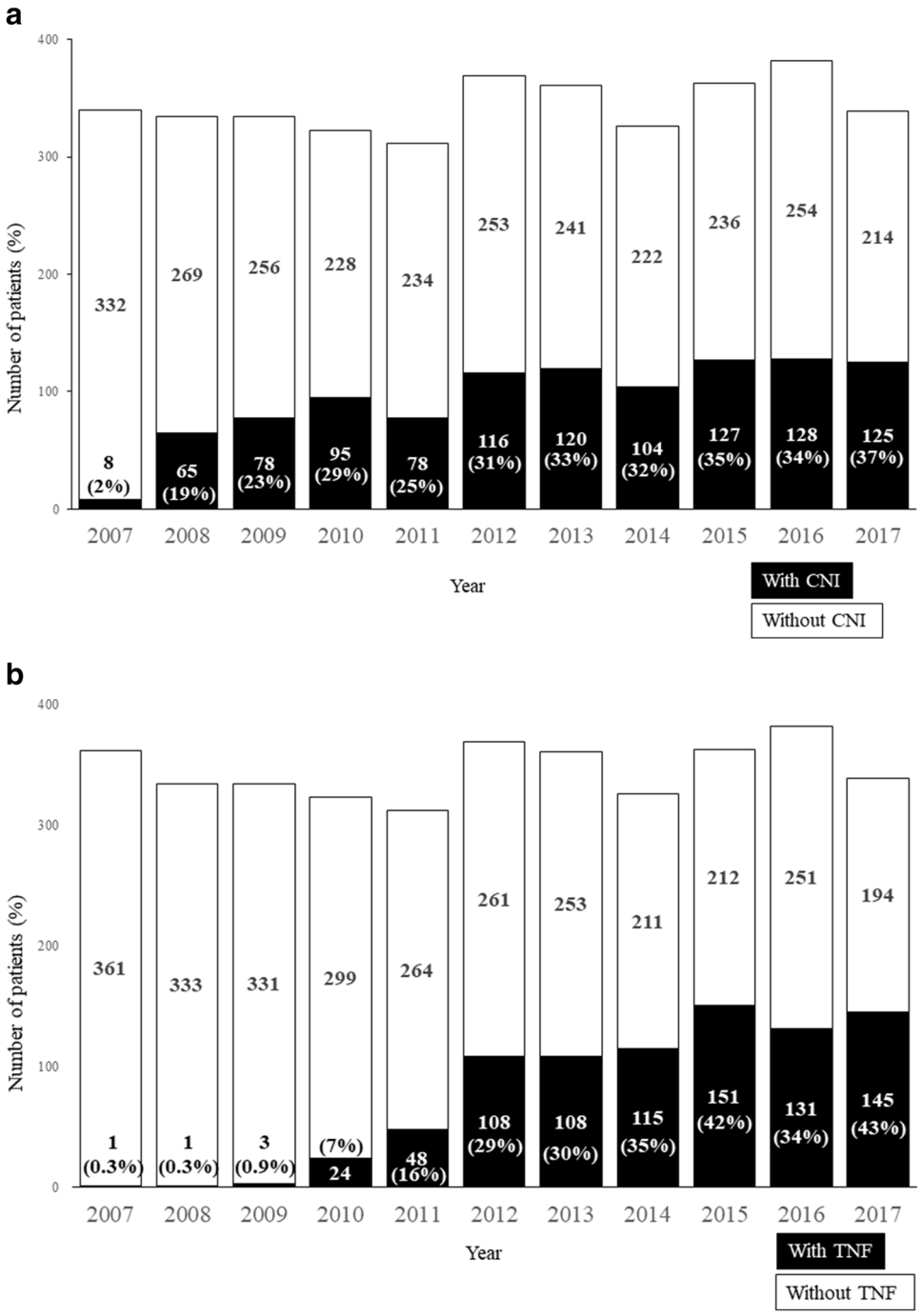

Fig. 3 **a** The incidence of calcineurin inhibitor (CNI) administration. **b** The incidence of anti-tumor necrosis factor (TNF)-α agent administration. The percentage is shown in parentheses. The rate of administration of CNI and anti-TNF increased from 8% and 0.3%, respectively, in 2007 to 37% and 43%, respectively, in 2017 ($p < 0.01$)

Timing of surgery

The changes in surgical timing are indicated in Fig. 4. The prevalence of each surgical timing did not change according to the era.

Indication for surgery

The changes in surgical indications are presented in Fig. 5. The most distinctive change in surgical indications is the recent increase in CAC. The prevalence of CAC increased from 20.2% in 2007 to 34.8% in 2017.

Discussion

The number of patients needing surgery for UC reportedly decreased temporarily soon after IFX and CNIs first became widely available but subsequently increased again in 2013 [16]. Those findings were derived from a survey that included questionnaires distributed to 16 Japanese institutions between 2008 and 2013.

In the present study, we analyzed data from 2007 to 2017 collected via a questionnaire survey from 21 institutions. Similar to previous reports in Sweden and Canada,

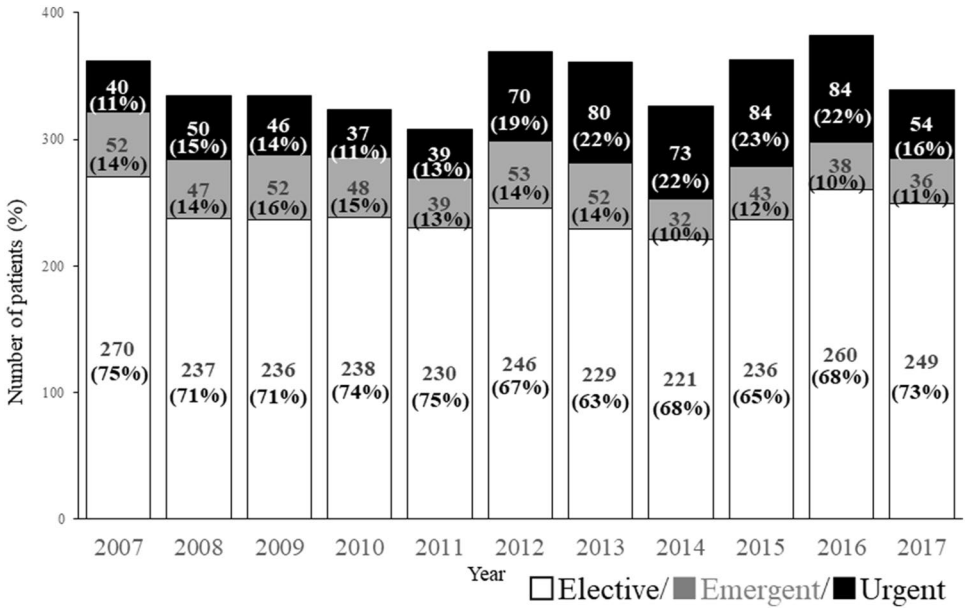

Fig. 4 Timing of surgery. The percentage is shown in parentheses. The surgical timing did not change markedly ($p=0.97$)

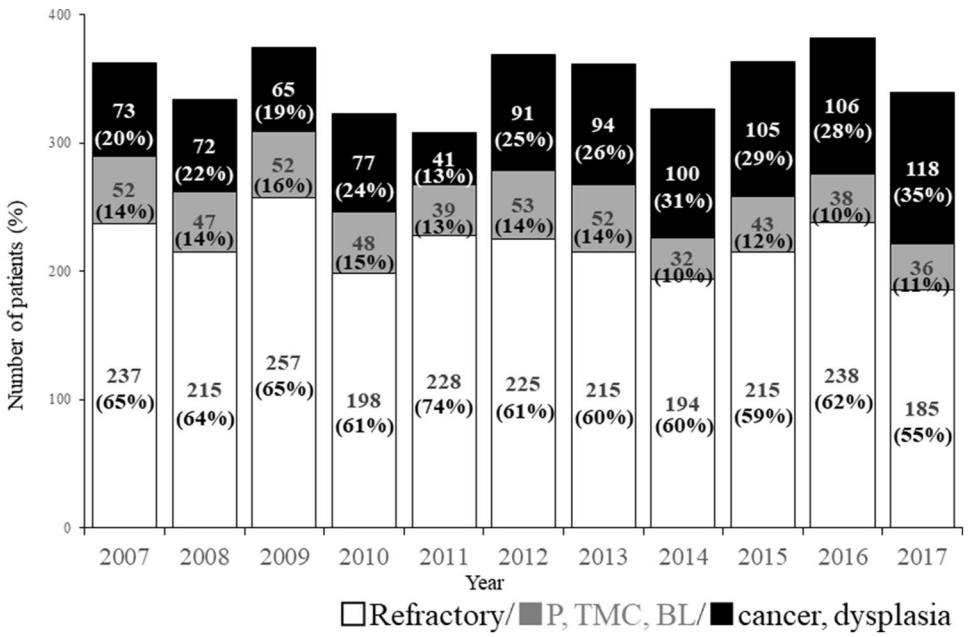

Fig. 5 Indications of surgery. The percentage is shown in parentheses. The rate of cancer/dysplasia significantly increased from 20.2% in 2007 to 34.8% in 2017 ($p=0.02$). *P* perforation, *TMC* toxic megacolon, *BL* massive bleeding

the incidence of elective colectomy for UC also decreased according to this survey during the era of anti-TNF agents and CNIs [2, 3, 17]. However, these advanced treatments for UC had no efficacy in preventing urgent/emergent surgery for severe UC. They may have been more effective for managing mild or moderate disease activity in patients with refractory UC than severe or fulminant UC. According to a systematic review that compared and demonstrated the efficacy of anti-TNF agents and CNIs for severe steroid-refractory UC, the rates of rescue efficacy were 62.4% for response and 38.9% for remission in 314 participants. However, the colectomy rates were high, including 28.3% at 3 months and 42.3% at 12 months [18]. Therefore, urgent surgery for UC flares and refractory UC might be required and may not be decreasing with progress in treatments.

Elective surgeries for UC did decrease during the era of treatment with anti-TNF agents and CNIs. While these agents might be associated with rescue therapy preventing colectomy, they can lead to a long disease duration of UC. Patients with long-standing UC are at a higher risk than the general population of developing CAC. The prevalence of this cancer was reported to be 8% 20 years after the initial UC diagnosis and increased to 18% at 30 years [19]; it is a major cause of mortality in patients with UC [20, 21]. In this series, although elective surgeries decreased with advanced treatments, the incidence of surgical indication with CAC was significantly increased. Although a direct association between anti-TNF agents or CNIs and carcinogenesis could not be proven in this study, long-standing UC is associated with a high risk for CAC, and valuable chemopreventive treatments for inflammation may create a high risk for carcinogenesis as a double-edged sword.

Although the prevalence of PSL use did not markedly change historically, the total administered dose and daily dose both decreased significantly at a single high-volume center, while the disease duration did not change. This decrease seems to coincide with the increasing prevalence of CNIs and anti-TNF agents. These results might have been due to the proper use of PSL for refractory UC.

Several limitations associated with the present study warrant mention. First, this survey did not include complete data on the incidence or number of surgeries associated with UC in Japan. The questionnaire survey targeted surgical departments. We did not consider or collect the total number of overall patients with UC who had not been surgically treated. The rate of colectomy may change when all patients are included, although we used the national records of Japanese UC patients collected nationwide by the Ministry of Health, Labour and Welfare in Japan since 1975 for the analysis of the prevalence. These data seem to reflect the actual number of UC patients because the government guarantees free treatment for UC in Japan; however, these may be incomplete data that do not reflect patients who did not visit a medical institution or who were not recorded. Furthermore, the actual number of overall surgeries might not be included. All institutions in this study are leading institutions for inflammatory bowel disease; however, surgical cases of UC at minor institutions might not have been included, although the majority of RPCs were able to be collected from the NCD [14]. The number of UC surgeries in the NCD records accounted for 70–100%, as indicated in Table 1. In Japan, RPC is performed only for UC and FAP. The number of surgeries for FAP between 2000 and 2012 was reported to be 319 cases in a Japanese FAP survey [22]. Therefore, we considered that this survey might reflect the real number of surgeries for UC.

We did not use the NCD data for two reasons: first, we were unable to use individual NCD data. Second, NCD data do not include patient information regarding treatment history and surgical indications. Therefore, we used a questionnaire for the evaluation.

As the second limitation, the questionnaire assessed only the number of UC surgeries, their indications and timing and the history of immunosuppressive agent use. In this retrospective, multicenter questionnaire setting, the collection of data regarding age, disease onset, duration of disease until colectomy, dosages of administered immunosuppressive agents, or use of surgical procedures was difficult, even though these parameters may have affected and reflected surgical trends. These parameters should be collected in a further prospective study using a commonly created database.

As the third limitation, the decreasing rate of elective surgery may not have been influenced solely by anti-TNF agents or CNIs. Skill in providing UC care has increased with multi-disciplinary teams that include cooperation among physicians and surgeons, IBD nurses, pharmacists, clinical engineers, or nutritionists or patient education, and this may be associated with the prevention of colectomy for worsened UC during the study period.

In conclusion, the prevalence of UC surgery seems to be decreasing according to the increasing rate of anti-TNF agent and CNI administration. Furthermore, PSL use seems to be optimized. However, the rate of urgent/emergent surgery did not decrease, and the indication of CAC significantly increased. Further research should evaluate whether or not long-term remission maintained with several agents can lead to an increase in CAC.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with this study.

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