Questionnaire-Based Survey on Management of Ulcerative Colitis-Associated Cancer in East Asian Countries

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Keywords

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Abstract

Background/Aims: To elucidate the current management of ulcerative colitis (UC)-associated cancer, a questionnaire-based survey was conducted to gather current opinions on colitis-associated cancer in different East Asian countries.

Methods: The questionnaire, based on physicians, contains 9 questions focused on UC management and cancer surveil-

lance. In addition, the questionnaire based on neoplastic cases, which contains 17 questions, was collected and analyzed. **Results:** With regard to the diagnosis of UC-associated cancer, most respondents started surveillance colonoscopy within 10 years from onset, favored targeted biopsies, and thought advanced imaging was useful. As for morphology, the frequency of elevated lesion and type 4 lesions was most common in early and advanced cancer, respectively. Peritoneal metastasis was frequently observed, and undifferentiated tumor was frequently developed. Laparoscopic surgery was widely used because it is less invasive. The prognostic outcome was poor, particularly in stage III and undifferenti-

ated type. **Conclusions:** The current survey elucidated the current management in Asian countries and characteristics of colitis-associated cancer in these countries.

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Introduction

The prevalence and incidence of ulcerative colitis (UC) are lower in East Asia than in Western countries. However, marked increases have been recently reported. Although the prognosis of UC is generally good, the mortality rate increases once colon cancer has developed. Several reports described that the estimated risk of UC-associated cancer at 10, 20, and 30 years is 0.5–2%, 1.1–8%, and 18%, respectively [1–3]. Overall, the incidence of UC-associated colorectal cancer (CRC) has been increased in those areas [4]. Colitis-associated CRC does not present the adenoma-carcinoma sequence, which is typical of sporadic CRC, and the clinicopathological characteristics were different compared to sporadic CRC [5]. To elucidate the current management of UC-associated cancer, a questionnaire-based survey was conducted to gather current opinions on colitis-associated cancer in different East Asian countries.

Subjects and Methods

Participants

A questionnaire was provided by representative International Gastrointestinal Consensus Symposium committee members to selected physicians in each country, starting in July 2017. Responses were collected by electronic mail until the end of November 2017. The questionnaire contains 9 questions focused on UC management and cancer surveillance. In addition, the questionnaire based on neoplastic cases, which contains 17 questions, was collected and analyzed. The questionnaire is attached in the Appendix.

Statistical Analysis

Continuous variables were expressed as mean or median, as appropriate. Categorical variables were presented as number and percentage. The prognostic comparison between groups was performed using the log-rank test. All statistical analyses were performed using the R statistical software.

Results

Physician's Survey

The respondents are from China, Hong Kong, Indonesia, Japan, South Korea, Philippines, Singapore, and Thailand. Table 1 shows the number of respondents

Table 1. Number of physicians who participated in this questionnaire-based survey

Country	Number	Specialist on IBD	Non-specialist on IBD	ND
China	21	15	6	0
Hong Kong	20	7	13	0
Indonesia	29	19	9	1
Korea	24	23	1	0
Japan	106	67	38	1
Philippines	29	1	27	1
Singapore	1	1	0	0
Thailand	20	3	17	0
Total	250	136	111	3

IBD, inflammatory bowel disease; ND, not determined.

from each country and their specialty in inflammatory bowel disease (IBD). The total number of respondents is 250 physicians. Most of the respondents belonged to a university, hospital, or clinic. A total of 106 respondents were from Japan, approximately 30 respondents from Indonesia and Philippines, and approximately 20 respondents from China, Hong Kong, Korea, and Thailand. With regard to their specialty, the ratio of specialist is relatively high in China, Indonesia, Korea, and Japan.

Figure 1 shows the number of patients with UC in the respondent's institution. The boxplot presented the number of patients with UC. In China, Japan, and Korea, one institution manages 200–300 patients. Approximately, 80 and 20 patients were treated per institution in Hong Kong and Indonesia, and the Philippines and Thailand, respectively.

Surveillance colonoscopy is necessary to detect neoplasia in patients with UC. Figure 2 shows the timing for the initiation of surveillance colonoscopy. The boxplot shows years from onset. The median ranged from 5 to 10 years from onset. Figure 3 shows the methods of biopsy. The ratio differs in each country. The ratio of random biopsy was relatively high in the Philippines and Thailand. However, approximately 70% of respondents favored targeted biopsies. Subsequently, the item regarding the number of cases detected in the last 5 years was included. Each respondent detected few colitis-associated cancers per year as shown in Figure 4. The usefulness of advanced imaging colonoscopy is shown in Figure 5. Approximately, 80% of respondents thought that advanced imaging was useful in detecting neoplasia compared with white light endoscopy.

Fig. 1. Number of patients with UC in the respondent's institution is presented by the boxplot. The median is noted below the column.

Fig. 2. Years from onset to starting surveillance colonoscopy in respondents are shown by the boxplot. The median is noted below the column.

Case Survey

In addition to the questionnaire, a case-based study was conducted using the given clinical information. The total number of UC-associated cancer cases was 125. Table 2 shows the number of patients with UC-associated

cancer reported from each country, with 95, 11, and 9 patients from Japan, China, and Korea, respectively. The mean age was approximately 55 years, suggesting that the patients with UC-associated cancer were younger than those with sporadic CRC, and 60 and 40% were men and

Fig. 3. Ratio for strategies of biopsy the respondent performs.

Fig. 4. Numbers of patients with UC-associated cancer respondent detected in the last 5 years. The mean value is noted below the column.

women, respectively. The mean from the onset was 10–20 years in each country.

For further study, we analyzed the entire population because the number of patients was biased in some countries. Table 3 shows the patient characteristics. The mean age was 52 years. With regard to the type of UC, the majority of them were total and left colitis types. Most patients were administered 5-aminosalicylic acid, with 50% administered steroid, 25% azathioprine, and 10% anti-

TNF α antibody. Twenty-five lesions developed in the right colon, including the cecum, ascending colon, and transverse colon, whereas 108 lesions developed in the left colon, including the descending colon, sigmoid colon, and rectum. With regard to the macroscopic type, the ratio of the elevated type is high in early cancer. Type 2, 3, and 4 lesions are the dominant types in advanced cancer. The ratio of type 4 lesions seems to be higher than that of sporadic CRC. The mean tumor size was 39 mm

Table 2. Number of neoplastic cases

Country	Number of cases	Age, years, mean (range)	Gender, male:female	Years from onset mean (range)
China	11	53.9 (38–70)	8:3	17.1 (0–31)
Hong Kong	3	57.7 (41–68)	3:0	19.7 (15–23)
Indonesia	5	53.4 (48–64)	5:0	11.2 (3.5–25)
Japan	95	52.0 (7–87)	53:42	17.6 (1–59)
Korea	9	47.3 (30–78)	6:3	16.4 (4–35)
Philippines	1	NA	0:1	3
Thailand	1	50	1:0	15
Total	125

Fig. 5. Ratio of advanced imaging the respondent thought to be effective.

in diameter. With regard to the histology, 57 were tubular differentiated type, and approximately 10 were poorly or signet ring cell or mucinous carcinoma. The extent of cancer was also reported. Half of the available cases were advanced cancer, and 25 cases were lymph node metastasis, 2 cases were hepatic metastasis, 7 cases were peritoneal dissemination, and 3 cases were distant metastasis. The frequency of peritoneal dissemination seemed high.

Subsequently, we summarized the treatment for cancer. Nine patients were selected to undergo endoscopic treatment (Table 4), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Most of them were in situ carcinoma. Surgical treatment was selected in 79 cases. Chemotherapy was selected or added in 10 patients. Radiotherapy was selected, particularly for patients with advanced rectal cancer. In 79 patients who underwent surgery, laparoscopic

surgery, total colectomy, and hand-sewn anastomosis were performed in 53, 88, and 52%, respectively.

Subsequently, we performed survival analyses. With regard to stage, stage III has a worse prognosis than stages I and II cancer. The 5-year overall survival in stage III cancer seemed to be worse than that in sporadic CRC (Fig. 6a). No significant difference was observed between the left- and right-sided UC-associated cancer (Fig. 6b). Poorly, signet ring cell, and mucinous tumors were developed in 10% of all patients, and these tumors showed a significantly poorer prognosis than the differentiated type (Fig. 6c).

Discussion

In this study, a survey was conducted to determine the current management of colitis-associated cancer in East Asia. With regard to the diagnosis of UC-associated can-

cer, most respondents started surveillance colonoscopy within 10 years from onset, and favored targeted biopsies, and thought that advanced imaging was useful. With regard to the macroscopic findings, elevated lesion was most frequently observed in early cancer, and the frequency of type 4 lesions was high. Metastatic behavior, such as peritoneal metastasis, was frequently observed. Laparoscopic surgery was widely used because it is less invasive. The prognostic outcome was poor, particularly in those with stage III cancer. No significant difference was observed regarding the location of the tumor, and the undifferentiated type showed poorer prognosis than the differentiated type.

The morphology of colitis-associated cancer differs from sporadic CRC. Colitis-associated cancer often occurs as a widespread type. This feature makes identification of dysplastic lesions difficult when the tumor elevation and size is not large [6]. For this reason, advanced imaging was applied to colonoscopy surveillance. In this study, 70% of respondents favored advanced imaging. However, the clear benefit of narrow band imaging over conventional white light endoscopy or chromoendoscopy was not elucidated [7]. Recently, the SCENIC international consensus statement on surveillance and management of dysplasia in IBD was reported [8]. In the guideline, narrow-band imaging is not suggested as an alternative for white-light colonoscopy and chromoendoscopy to detect dysplasia. With regard to the surveillance method, target biopsy under pan-chromoendoscopy is preferentially recommended compared to random biopsy [9].

The behavior of colitis-associated cancer differs from that of sporadic CRC. Colitis-associated cancer often occurs multifocally. Therefore, performing total proctocolectomy is recommended if any dysplastic or cancerous lesions are identified in patients with UC [6]. In this survey, 21% of patients underwent partial colectomy or endoscopic resection. Detailed information regarding the reason of the decision could not be obtained. The decision was suggested to be made for defecation function preservation. Laparoscopic surgery was performed in 53% of patients in East Asia. The merit of laparoscopic surgery is a magnified view of the surgical sites, and less traumatic abdominal wall. Overall, laparoscopic surgery and hand-assisted surgery both have a non-inferiority to open proctocolectomy regarding cosmetic results, quality of life, and functional outcome [10–12]. Moreover, the method of anastomosis was surveyed. A meta-analysis comparing hand-sewn versus stapled anastomosis revealed that both had similar outcomes. However, stapled

Table 3. Characteristics of patient

Characteristics		<i>n</i> = 125
Age, years	52	(7–87)
Gender		
Male	76	
Female	49	
Type of UC		
Total colon	92	
Left colon	31	
Rectum	2	
Medication		
5-ASA	121	
Steroid	61	
AZA	33	
TNFa	13	
IM	6	
Location		
Cecum	5	
Ascending	12	
Transverse	8	
Descending	15	
Sigmoid	35	
Upper rectum	30	
Lower rectum	28	
Macroscopic type		
Early		
Polypoid	14	
Elevated	41	
Flat	18	
Depressed	7	
Advanced		
Type 1	8	
Type 2	13	
Type 3	11	
Type 4	12	
Type 5	6	
Size, mm	39	(5–280)
Histology		
Tubular	57	
Poorly	4	
Signet ring cell	2	
Mucinous	5	
Depth of invasion		
~0	22	
1	15	
2	15	
3	15	
4	10	
Lymph node metastasis		
Absent	59	
Present	25	
Liver metastasis		
Absent	80	
Present	2	
Peritoneal metastasis		
Absent	76	
Present	7	
Distant metastasis		
Absent	78	
Present	3

Fig. 6. Survival curves for (a) based on stage, (b) tumor location, and (c) histological types.

Table 4. Treatment of cancer

Treatment	
Endoscopic resection	1
EMR	
ESD	8
Surgical resection	79
Chemotherapy	10
Radiotherapy	2
Surgical cases	(<i>n</i> = 79)
Approach	
Open	34
Laparoscopy	39
Procedure	67
Total proctocolectomy	
Partial colectomy	9
Anastomosis	29
Hand-sewn anastomosis	
Stapler anastomosis	27

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

anastomosis improved sleeping, with higher anorectal physiologic testing. A risk of increased incidence of dysplasia in the cuff may exist in stapled anastomosis [13]. The method of anastomosis should be carefully considered because of the risk of bowel function impairment versus the risk of long-term dysplasia caused by ongoing inflammation in the retained rectal mucosa.

Colitis-associated cancer often invades to the deeper layers of the bowel wall from an earlier stage of progression. Poorly differentiated adenocarcinoma and mucinous carcinoma also tend to develop in UC [14]. These undifferentiated tumors show a poorer prognosis in the present study. For these reasons, the relative worse prognosis was accounted particularly in stages II and III cancers. In the present study, the 5-year overall survival was 40% in stage III. Watanabe et al. [15] reported that the prognosis of sporadic stage III CRC in Japan accounted for 52.9–83.0%. A recent report discussed prognostic differences in left and right colon cancers [16]. However, in the present survey, no significant difference was observed regarding the location of the tumor in UC-associated cancer.

The limitation of the present study was the small number of cases, and the majority of the cases were biased to

some countries. In conclusion, a questionnaire-based survey was conducted to gather current opinions on colitis-associated cancer in different East Asian countries. The current survey elucidated the current management in Asian countries and characteristics of colitis-associated cancer in these countries.

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Appendix

Questionnaire: Diagnosis and treatment of ulcerative colitis-associated colorectal cancer in Asia

Your institution ()

1. Please indicate your country. ()
2. Are you a specialist in IBD? (☐Y / ☐N)
3. How many UC patient do you treat in your institution in one year? () patients
4. What is your first choice for the treatment of newly diagnosed UC?
☐5-ASAs ☐steroid ☐AZA ☐Anti-TNF ☐immunomodulator
☐Others (describe:)
5. Cancer surveillance
When do you start the surveillance colonoscopy for UC patients to detect neoplasia?
() years from onset
6. Which of the strategies for surveillance colonoscopy do you perform?
☐random biopsies ☐targeted biopsies ☐other
7. How many colitis cancer patients did you detect/diagnose in last the 5 years?
() patients
8. Do you think that color enhancement or narrow band imaging colonoscopy is useful to detect colitis cancer? (☐Y / ☐N)

9. Please indicate the proportion of the indication for surgery in your UC patients?

()% for neoplasia / ()% for severe or refractory colitis

If you have experienced ulcerative colitis-associated colorectal cancer case in past 5 years, please describe the next questionnaire in each patient.

Your country () Your institution ()

Arbitrary case number ()

1. Age () years old
2. Gender ☐Male ☐Female
3. Years from onset of UC () years
4. Type of UC ☐total colon ☐left colon ☐rectum
5. What kind of treatment did you administer in this patient?
☐5-ASAs ☐steroid ☐AZA ☐Anti-TNF ☐immuno-modulator ☐Others (describe:)
6. Location of neoplasia ☐Cecum ☐Ascending ☐Transverse ☐Descending ☐Sigmoid ☐Upper Rectum ☐Lower Rectum
7. How many times did you do surveillance colonoscopy to detect this neoplasia? () times
8. Macroscopic types (early cancer) ☐polypoid ☐elevated ☐flat ☐depressed
9. Macroscopic types (advanced cancer) ☐Borrmann1 ☐2 ☐3 ☐4 ☐5
10. Tumor size () mm
11. Histological types ()
12. Depth of tumor invasion ()
13. Metastatic lesions
Lymph node metastasis (Regional lymph nodes) ☐positive ☐negative
Liver metastasis (H) ☐positive ☐negative
Peritoneal metastasis (P) ☐positive ☐negative
Extrahepatic distant metastasis (M) ☐positive ☐negative
14. According to UICC TNM classification T () N () M ()
15. Treatment ☐Endoscopic treatment (☐EMR ☐ESD) ☐Surgical treatment ☐Chemotherapy ☐Radiotherapy
If available, please describe below
Approach to the lesion ☐open ☐laparoscopic
Surgical procedures ☐total colectomy ☐partial colectomy
Anastomosis ☐Hand-sewn ☐stapler
16. Adjuvant therapy ☐Non ☐Chemotherapy ☐Radiotherapy
17. Prognosis ☐Alive () months from intervention ☐Dead () months from intervention.

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