BMJ Open Gastroenterology

Comparison of outcomes between symptomatic and asymptomatic patients with colorectal cancer: a propensity score-matched analysis of surgical invasiveness, medical costs and oncological outcomes

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To cite: Inada R, Nagasaka T, Watanabe A, *et al*. Comparison of outcomes between symptomatic and asymptomatic patients with colorectal cancer: a propensity score-matched analysis of surgical invasiveness, medical costs and oncological outcomes. *BMJ Open Gastro* 2017;**4**: e000146. doi:10.1136/bmjgast-2017-000146

Received 28 March 2017
Revised 22 May 2017
Accepted 3 June 2017

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ABSTRACT

Background and aims: Whether asymptomatic patients with colorectal cancer (CRC) who are treated in hospitals show better outcomes than symptomatic patients with CRC still remains unknown. The aim of this study was to evaluate differences in clinical benefits following treatment in asymptomatic and symptomatic patients with CRC.

Methods: This study was a retrospective cohort analysis with data obtained from records. A cohort of 145 asymptomatic and 123 symptomatic patients who underwent CRC surgery between January 2009 and December 2011 was enrolled. To reduce bias in comparing outcomes, propensity score (PS) analysis was used for matching of patients in the symptomatic and asymptomatic groups based on clinicopathological factors. Surgical invasiveness, medical costs and oncological outcomes were examined by unadjusted and PS-matched analysis.

Results: Tumours in the symptomatic group were more often diagnosed in advanced stages compared with tumours in the asymptomatic group. Therefore, fewer symptomatic group patients underwent minimally invasive surgery. Short-term outcomes, including amount of blood loss, duration of postoperative hospital stay and perioperative medical costs, were significantly better in the asymptomatic group. Although overall survival was significantly better in the asymptomatic group, there was no significant difference between the groups when the patients were adjusted on the basis of PS.

Conclusions: Though this study was limited by the retrospective nature and small sample size, favourable outcomes in asymptomatic patients were due to the higher proportion of patients in this group who were diagnosed with CRC in earlier stages, due to participation in CRC screening programmes.

Summary box

What is already known about this subject?

- Although previous randomised controlled trials (RCTs) of CRC screening showed its benefits, especially with respect to long-term oncological outcomes and cost-effectiveness, to the best of our knowledge, the benefits observed in people enrolled in CRC screening programmes is based on mass screening of a large population. No study has evaluated the effectiveness of CRC screening in relation to postoperative outcomes.

What are the new findings?

- This study shows that participating in some kind of colorectal cancer (CRC) screening programme will facilitate the diagnosis of CRC in its early stages, while patients are still asymptomatic, leading to better long-term oncological outcomes and cost-effectiveness.

How might it impact on clinical practice in the foreseeable future?

- By comparing clinical outcomes in symptomatic patients with CRC with those in asymptomatic patients, we showed that asymptomatic patients with CRC had superior short-term perioperative outcomes, as well as long-term oncological outcomes, mainly owing to the greater opportunity for undergoing minimally invasive surgeries.

INTRODUCTION

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in men and the second in women.[1] In terms of the number of cancer-related deaths, CRC is the fourth most common cause of death in men and the third in women, with 693 900 deaths/

year.[1] Although the incidence rates of CRCs vary according to region and have been increasing mainly in developing countries,[1 2] CRC-related deaths have been decreasing in many countries.[3 4] Indeed, many large-scale, randomised controlled trials (RCTs) have shown that systematic CRC screening programmes reduce overall mortality.[5–13] Therefore, many countries, especially developed countries, are now making systematic CRC screening programmes available to a large section of society. While better outcomes of CRC screening programmes were demonstrated by RCTs involving large populations, this benefit was apparent only in large populations, and not to all the individuals who participated in the CRC screening programmes.

Patients diagnosed with CRC after experiencing subjective symptoms are generally thought to have advanced tumours and, therefore, to have poorer prognosis compared with patients with asymptomatic colorectal tumours. Besides, these symptomatic patients are less likely to have undergone CRC screening and have more unfavourable short-term outcomes postoperatively. Previous RCTs of CRC screening showed its benefits, especially with respect to long-term oncological outcomes and cost-effectiveness.[5–19] However, to the best of our knowledge, the benefits are observed in people enrolled in CRC screening programmes, which are based on mass screening of a large population. No study has evaluated the effectiveness of CRC screening in relation to postoperative outcomes.[5–13]

In this study, by comparing clinical outcomes in symptomatic patients with CRC with those in asymptomatic patients, we tried to determine the effectiveness of CRC screening in a small population.

MATERIALS AND METHODS

Patients

This study was designed as a single-centre, retrospective, observational analysis of symptomatic and asymptomatic patients with CRC. The study was approved by the institutional review board of Okayama University Hospital, Okayama, Japan. All patients gave their informed consent for use of their data for analysis.

Between January 2009 and December 2011, a cohort of 268 patients who had undergone surgical resection for CRC in Okayama University Hospital, Okayama, Japan, was enrolled. Of the 268 consecutive patients, 145 patients were diagnosed while asymptomatic, and 123 patients were diagnosed after developing symptoms. Among them, five patients underwent only palliative stoma creation or bypass operations.

Tumour stage was evaluated before surgery by clinical investigations, including total colonoscopy, chest X-rays, abdominal ultrasonography and CT. The selection criterion for laparoscopic surgery was preoperative diagnosis of T1, T2 or T3 CRC. Patients with T4 CRC preoperatively, bulky tumours (>8 cm), history of extensive adhesions, severe obesity (body mass index (BMI) >30 kg/m^2) and intestinal obstruction underwent open surgery. Those who did not consent to laparoscopic surgery also underwent open surgery. Laparoscopic surgery was converted to laparotomy if open techniques were needed to manage unexpected intraoperative difficulties. Patients requiring conversion to laparotomy were classified as open surgery cases in this study. Adjuvant chemotherapy was basically performed for patients with pathological stage III cancer by UICC TNM staging, if their performance status was 0 or 1. Patients with distant metastases (stage IV) underwent surgical resection of the distant metastatic sites when the metastatic tumour could be resected curatively.

Clinical data

The clinical parameters examined in this study were as follows: initial symptoms in the symptomatic patients, screening methods in the asymptomatic patients, age, sex, BMI, the American Society of Anesthesiologists Physical Status (ASA-PS) class, history of laparotomy, prognostic nutritional index (PNI), serum carcinoembryonic antigen (CEA) level, tumour location, pathological TNM stage (UICC 7th edition), surgical procedure (laparoscopic surgery or open surgery), length of operation, amount of blood loss, intraoperative transfusion, postoperative intensive care unit (ICU) management, length of hospital stay, mortality and morbidity (Clavien-Dindo classification of surgical complications).[20]

Statistical analysis

All statistical analyses were performed using SPSS V.23.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as medians (IQR) and were compared by the Mann-Whitney U test. Categorical variables were compared by Fisher's exact test. Overall survival curves were obtained using the Kaplan-Meier method and differences in survival times among subgroups were compared using the log-rank test. HRs with 95% CIs were calculated from Cox regression models. Multivariate analysis was performed to determine

Table 1 Initial symptoms in the symptomatic group and screening methods in the asymptomatic group

Initial symptom in the symptomatic group (n=145)	
Bloody stool	56
Abdominal pain	27
Abdominal distension	8
Nausea	3
Diarrhoea	8
Constipation	20
Narrow-calibre stool	4
Anal pain	1
Anal tumour palpation	2
Weight loss	4
Fatigue	10
Pneumaturia	1
Bone pain	1
Screening methods in the asymptomatic group (n=123)	
Faecal occult blood testing	72
Colonoscopy	17
CT scan	12
Positron emission tomography scan	3
Anaemia	13
High serum tumour marker level	6

the associations between clinicopathological variables and overall survival time. In addition to all-case comparison, propensity score (PS)-matched analysis was applied to reduce the possibility of bias. PS was calculated from a logistic regression model to fit with variables, including age, sex, ASA-PS, tumour location, TNM staging and residual disease. Then, symptomatic patients were matched 1:1 with asymptomatic patients, based on the closest propensity score. p Values of <0.05 were considered significant.

RESULTS

Patient characteristics

The present study included 145 symptomatic (symptomatic group) and 123 asymptomatic patients with CRC (symptomatic group). The initial symptoms observed in the symptomatic group and screening modalities used before a confirmed diagnosis of CRC in the asymptomatic group are shown in table 1. In the symptomatic group, the most common initial symptom was bloody stools, and the second was abdominal pain. In the asymptomatic group, faecal occult blood testing (FOBT) was the most common CRC screening procedure (58.5%).

The clinicopathological features in the two groups are presented in table 2. In the unadjusted cohort, there were no significant differences in age, sex and BMI between the two groups. ASA-PS was significantly higher (p=0.004) and PNI was significantly lower (p=0.005) in the symptomatic versus the asymptomatic group. In

Table 2 Clinicopathological features of symptomatic and asymptomatic patients with colorectal cancer

	Overall			After matching		
	Symptomatic patients (n=145)	Asymptomatic patients (n=123)	p Value	Symptomatic patients (n=80)	Asymptomatic patients (n=80)	p Value
Age (years)			0.95			0.93
Median (IQR)	67 (60–73)	67 (60–75)		67 (60–73)	67 (59–74)	
Sex			0.53			1.00
Male	82 (56.6%)	75 (61.0%)		40 (50.0%)	40 (50.0%)	
Female	63 (43.4%)	48 (39.0%)		40 (50.0%)	40 (50.0%)	
BMI (kg/m^2)			0.68			0.93
Median (IQR)	22.2 (19.7–24.5)	22.4 (20.1–24.2)		21.9 (19.4–24.4)	21.6 (19.0–24.2)	
ASA-PS			0.004			1.00
1, 2	133 (91.7%)	122 (99.2%)		79 (98.8%)	79 (98.8%)	
3, 4	12 (8.3%)	1 (0.8%)		1 (1.2%)	1 (1.2%)	
Prior abdominal operation			0.52			0.63
Present	53 (36.6%)	40 (32.5%)		33 (41.2%)	29 (36.3%)	
Absent	92 (63.4%)	83 (67.5%)		47 (58.8%)	51 (63.7%)	
PNI			0.005			0.23
Median (IQR)	49.2 (43.1–52.9)	50.7 (46.8–54.7)		50.2 (46.0–54.4)	51.1 (47.1–55.1)	
Serum CEA level (ng/mL)			0.004			0.66
Median (IQR)	4.0 (2.4–13.0)	3.2 (1.9–6.1)		3.1 (2.0–6.5)	3.6 (2.0–8.2)	
Tumour location			0.01			0.87
Colon	79 (54.5%)	88 (71.5%)		53 (63.3%)	51 (63.7%)	
Rectum	64 (44.1%)	35 (28.5%)		27 (33.7%)	29 (36.3%)	
Colon and rectum	2 (1.4%)	0 (0.0%)		0 (0%)	0 (0%)	
Primary tumour			<0.001			1.00
Tis, 1, 2	30 (20.7%)	63 (48.8%)		27 (33.7%)	28 (35.0%)	
T3, 4	115 (79.3%)	60 (51.2%)		53 (63.3%)	52 (65.0%)	
Lymph node involvement			<0.001			1.00
N0	65 (44.8%)	86 (69.9%)		44 (55.0%)	45 (56.3%)	
N1, 2	80 (55.2%)	37 (30.1%)		36 (45.0%)	35 (43.7%)	
Distant metastasis			<0.001			0.77
M0	113 (77.9%)	116 (94.3%)		75 (93.8%)	73 (91.3%)	
M1	32 (22.1%)	7 (5.7%)		5 (6.2%)	7 (8.7%)	
Stage			<0.001			1.00
Stage 0, I, II	62 (42.8%)	84 (68.3%)		43 (53.8%)	43 (53.8%)	
Stage III, IV	83 (57.2%)	39 (31.7%)		37 (46.3%)	37 (46.3%)	
Residual disease			<0.001			1.00
Negative	116 (80.0%)	118 (95.9%)		74 (92.5%)	75 (93.8%)	
Positive	29 (20.0%)	5 (4.1%)		6 (7.5%)	5 (6.2%)	

ASA-PS, American Society of Anesthesiologists-physical status; BMI, body mass index; CEA, carcinoembryonic antigen; PNI, prognostic nutritional index.

Table 3 Intraoperative and postoperative outcomes in the symptomatic and asymptomatic patients with colorectal cancers

	Overall			After matching		
	Symptomatic patients (n=145)	Asymptomatic patients (n=123)	p Value	Symptomatic patients (n=80)	Asymptomatic patients (n=80)	p Value
Surgical procedure			<0.001			0.03
Laparoscopic surgery	30 (20.7%)	71 (57.7%)		21 (26.3%)	35 (43.85%)	
Open surgery	115 (79.3%)	52 (42.3%)		59 (73.7%)	45 (56.3%)	
Duration of operation (min)			0.15			0.57
Median (IQR)	215 (171–295)	200 (166–270)		215 (170–291)	210 (169–276)	
Amount of blood loss (mL)			<0.001			0.09
Median (IQR)	150 (20–310)	50 (1–130)		103 (9–235)	50 (5–150)	
Intraoperative transfusion			0.001			0.10
Required	20 (13.8%)	3 (2.4%)		8 (10.0%)	2 (2.5%)	
Not required	125 (86.2%)	120 (97.6%)		72 (90.0%)	78 (97.5%)	
Postoperative ICU management			0.003			0.19
Required	48 (33.1%)	21 (17.1%)		22 (27.5%)	14 (17.5%)	
Not required	97 (66.9%)	102 (82.9%)		58 (72.5%)	66 (82.5%)	
Duration of postoperative hospitalisation (days)			<0.001			0.30
Median (IQR)	16 (12–24)	12 (9–17)		14 (12–21)	13 (10–19)	
Medical costs during hospitalisation (US$)			<0.001			0.061
Median (IQR)	13 393 (10 610–16 782)	10 244 (8977–12 991)		12 425 (9919–15 139)	11 001 (9202–15 221)	

1 US$ =120 Japanese Yen.
ICU, intensive care unit.

terms of tumour location, cancer in the rectum was more frequently observed in the symptomatic group (p=0.01). Serum CEA levels (p=0.004) and TNM stages, including each of the T, N and M factors, were significantly higher in the symptomatic group (p<0.001 for each of them). More patients in the symptomatic group underwent palliative surgery (p<0.001). PS analyses for age, sex, ASA-PS, tumour location, TNM staging and residual disease indicated that all the covariates were well balanced, with no significant differences between the symptomatic (n=80) and asymptomatic groups (n=80) after matching.

Intraoperative and postoperative outcomes and medical costs

Intraoperative and postoperative outcomes in the two groups are shown in table 3. Of the 145 symptomatic patients in the unadjusted cohort, 30 patients underwent laparoscopic surgery and 115 patients underwent open surgery, including four patients in whom the laparoscopic procedure was converted to open surgery. Furthermore, three patients underwent palliative bypass surgery and two other patients underwent palliative stoma creation. On the other hand, 71 of the 123 asymptomatic patients underwent laparoscopic surgery, and 52 patients underwent open surgery, including two patients in whom laparoscopic surgery was converted to open surgery. Laparoscopic surgery was performed less often in the symptomatic group (p<0.001). There were no significant differences in operation time between the groups, but the amount of blood loss was significantly higher in the symptomatic group (p<0.001). More symptomatic patients required intraoperative blood transfusion as compared with asymptomatic patients (p=0.001). Postoperative management in the ICU was significantly more required in the symptomatic group (p=0.003). Therefore, the duration of hospitalisation was longer in the symptomatic group (p<0.001) and medical expenses during hospitalisation were higher in the symptomatic group compared with the asymptomatic group (US $13 393 vs US$10, 244, p<0.001).

PS analysis indicated that laparoscopic surgery was performed more often in the asymptomatic group than the symptomatic group (p=0.03). None of the other variables related to intraoperative and postoperative outcomes were significantly different between the two groups.

Mortality and morbidity

Postoperative mortality and morbidity data are presented in table 4. There were three deaths within 30 days after surgery in the symptomatic group; one due to portal vein thrombosis on the 19th postoperative day (POD), one due to sepsis from bacterial translocation on the 7th POD, and one due to rapid growth of the tumour on the 20th POD. There were no significant differences in mortality and morbidity rates (classified according to the Clavien-Dindo classification) between the two groups by

Table 4 Mortality and morbidity (Clavien-Dindo classification) in patients with colorectal cancer

	Overall			After matching		
	Symptomatic patients (n=145)	Asymptomatic patients (n=123)	p Value	Symptomatic patients (n=80)	Asymptomatic patients (n=80)	p Value
Mortality	3 (2.1%)	0 (0.0%)	0.25	0 (0.0%)	0 (0.0%)	1.00
Morbidity						
Grade 1, 2 morbidity						
Intestinal obstruction	11	6		4	3	
Anastomotic leakage	1	2		0	2	
Wound infection	3	3		3	2	
Intra-abdominal abscess	1	2		1	2	
Colitis	2	3		1	1	
Cholecystitis	0	1		0	1	
Catheter infection	4	2		1	0	
Urinary tract infection	2	1		1	0	
Pneumonia	1	1		1	1	
Meningitis	1	0		0	0	
Sepsis	1	1		1	1	
Anastomotic bleeding	1	2		1	2	
Intra-abdominal bleeding	1	0		0	0	
Cerebral haemorrhage	1	0		0	0	
Urinary dysfunction	2	0		0	0	
Ascites	1	0		1	0	
Delirium	4	6		3	4	
Atrial fibrillation	0	2		0	2	
Deep vein thrombosis	1	0		1	0	
Grade 3, 4 morbidity						
Anastomotic leakage	5	4		0	3	
Intestinal obstruction	2	1		2	1	
Intra-abdominal abscess	6	1		2	1	
Anastomotic bleeding	1	2		1	2	
Ascites	1	0		0	0	
Total number of patients with morbidities						
Grades 1–4	51 (35.2%)	37 (30.1%)	0.43	23 (28.8%)	26 (32.5%)	0.73
Grades 3–4	18 (12.4%)	8 (6.5%)	0.15	5 (6.3%)	7 (8.8%)	0.77

PS analysis, as well as in analyses using the unadjusted cohort.

Overall survival, estimated by Kaplan-Meier curves, in all stages are shown in figure 1A. The median follow-up period for all cases was 32.3 months (14.8–44.1 months). Patients in the symptomatic group showed a worse prognosis (the log-rank test: p<0.001, Cox regression model: HR of symptomatic to asymptomatic group: 3.42, 95% CI 1.59 to 7.41, p=0.002). There were no significant differences in overall survival between stage I–III patients over a median follow-up period of 33.0 months (16.2–45.4 months), as shown in figure 1B (the log-rank test: p=0.146, Cox regression model: HR of symptomatic to asymptomatic group: 1.92, 95% CI 0.78 to 4.72, p=0.153).

Kaplan-Meier curves for overall survival of the patients selected by PS analysis are shown in figure 1C and D. When the patients were stratified by tumour staging,

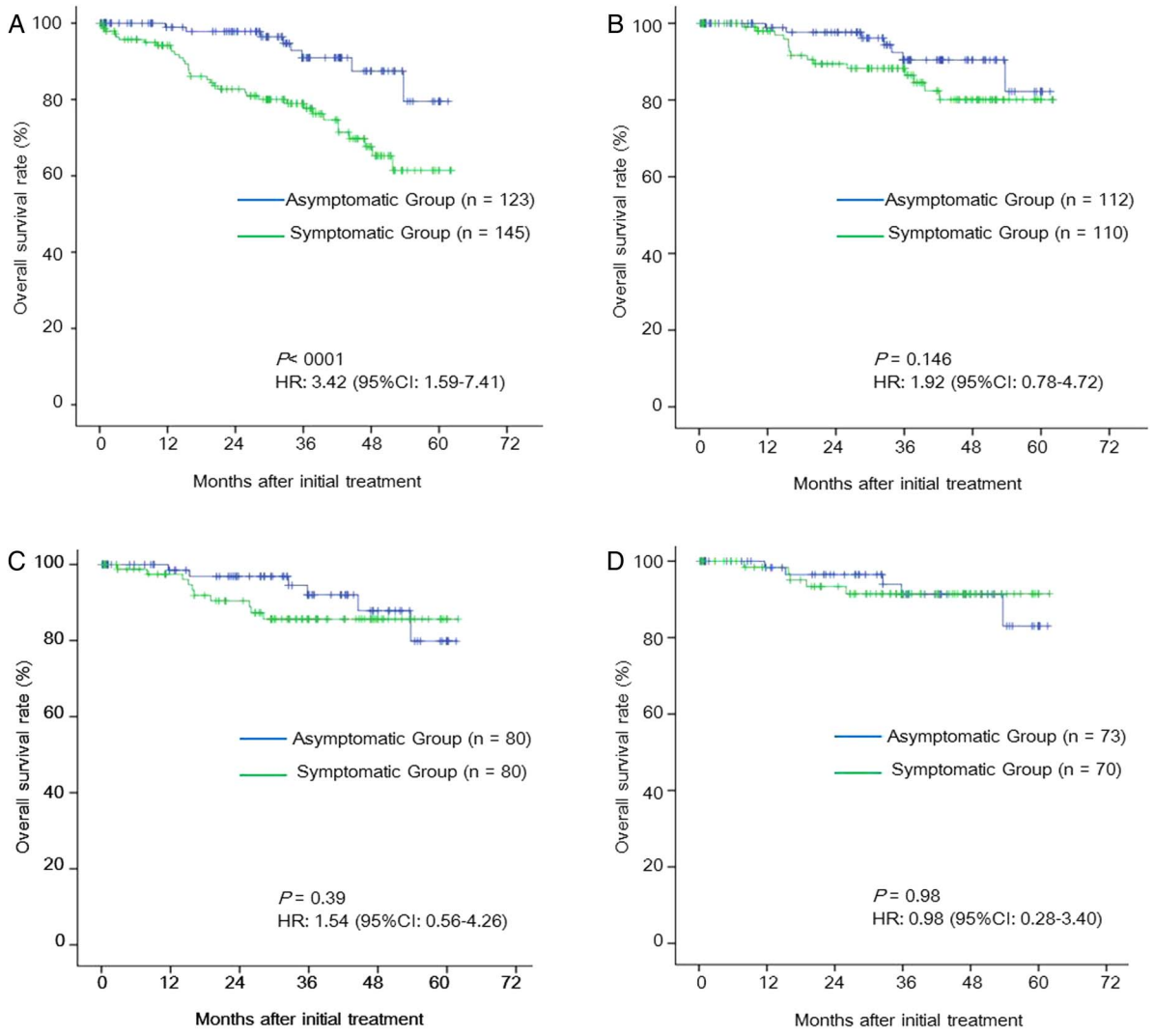

Figure 1 Overall survival curves in all the symptomatic and asymptomatic patients with colorectal cancer. (A) In an analysis of patients in all stages, symptomatic patients had a significantly worse prognosis than asymptomatic patients. (B) In an analysis of patients with stages I–III disease, there were no differences between the two patient groups. Overall survival curves in propensity score-matched symptomatic and asymptomatic patients with colorectal cancer. Analysis of patients in all stages of the disease (C) and those with stages I–III disease (D) indicated no differences between symptomatic and asymptomatic patient groups. p Values were calculated by the log-rank test.

there were no significant differences between the groups in all stages (figure 1C) and in stages I–III (figure 1D), (the log-rank test: p=0.39, Cox regression model: HR of symptomatic to asymptomatic group for all stages: 1.54, 95% CI 0.56 to 4.26, p=0.40, the log-rank test: p=0.98, Cox regression model: HR of symptomatic to asymptomatic group for stages I–III: 0.98, 95% CI 0.28 to 3.40, p=0.98).

Multivariate analysis of prognostic factors in all the 268 patients is shown in table 5. Lower PNI and residual disease were independent poor prognostic factors.

DISCUSSION

In this study, patients with asymptomatic tumours demonstrated better short-term outcomes and cost-effectiveness of treatment. However, these benefits observed in asymptomatic patients were no longer obvious when PS analysis matching for age, sex, performance status, tumour location, TNM staging and residual disease was used. Since the proportion of patients who participated in conventional CRC screening programmes was higher in the asymptomatic group, participating in CRC screening is thought to be beneficial for improving outcomes in CRC patients.

With respect to long-term outcomes, HR in the analysis using the unadjusted cohort of patients with stage I–III disease and from the PS analysis of overall stages and stage I–III disease were not significantly different. Multivariate analysis did not reveal symptom at the diagnosis as an independent prognostic factor. With respect to short-term outcomes, patients in the asymptomatic

Table 5 Cox regression analysis of prognostic factors in 268 patients with colorectal cancer

Variables	HR	95% CI	p Value
	Multivariate analysis		
Age (years)			
≥60/≤59	1.38	0.66 to 2.90	0.39
Sex			
Male/female	1.13	0.59 to 2.15	0.72
ASA-PS			
3, 4/1, 2	2.40	0.75 to 7.63	0.139
PNI			
<50/≥50	2.26	1.17 to 4.39	0.016
Serum CEA level (ng/mL)			
≥5.0/<5.0	0.83	0.41 to 1.69	0.61
Stage			
III, IV/0, I, II	1.59	0.69 to 3.71	0.28
Residual disease			
Positive/negative	8.93	4.03 to 20.00	<0.001
Symptom			
Present/absent	1.89	0.85 to 4.20	0.117

ASA-PS, American Society of Anesthesiologists-physical status; CEA, carcinoembryonic antigen; PNI, prognostic nutritional index.

group were more likely to undergo laparoscopic surgery. Postoperatively, patients in the asymptomatic group had a lesser need for ICU management and had shorter hospital stays. Medical costs during hospitalisation were significantly lower in the asymptomatic group. This could be because patients in the asymptomatic group were treated at an earlier stage of their disease. According to PS analysis, although laparoscopic surgery was performed more often in patients in the asymptomatic group, other variables related to short-term outcomes were not different between the groups.

In the asymptomatic group, FOBT was the most common CRC screening procedure, because FOBT is a standard, non-invasive, and low-cost screening procedure offered by the Japanese government. In the symptomatic group, bleeding and obstruction by primary tumours, presenting as bloody stools, pain, distention and constipation, were the common symptoms leading to the detection of CRCs. Tumours located in the rectum were more frequently observed in the symptomatic group, because distal tumours present with these symptoms earlier than tumours in the proximal colon. Patients with symptomatic tumours were diagnosed at later stages of the disease, were in poorer physical condition and had less opportunity for curative treatment. Therefore, the symptomatic group showed a significantly poorer prognosis compared with the asymptomatic group in the unadjusted cohort.

Patients with early-stage CRC have a greater chance of undergoing minimally invasive surgery while following oncological guidelines. Several large-scale RCTs reported that laparoscopic surgery for CRC was comparable or superior to open surgery with regard to long-term and short-term outcomes.[21–25] However, most of these trials excluded far advanced CRCs, including bulky tumours, T4 tumours and tumours with metastases; therefore, patients with such advanced CRCs were often not recommended laparoscopic surgeries due to the lack of technical feasibility and oncological radicality.

Currently, FOBT, colonoscopy, double-contrast barium enema and CT colonography are the usual CRC screening procedures available in Japan. Many large-scale RCTs evaluating CRC screening have indicated a reduction in the incidence of CRC and overall mortality.[5–12] CRC screening programmes using guaiac-based FOBT showed a significant reduction in CRC mortality rates.[5–10] Among them, the trial with the longest follow-up period (30 years) reported that mortality rates reduced by 32% after annual screening and by 22% after biennial screening.[10] Two RCTs also demonstrated that CRC screening with flexible sigmoidoscopy decreased the incidence rate of CRC and overall mortality rate.[11 12] In a larger trial with over 170 000 participants between the ages of 55 and 64 years, one-time screening with sigmoidoscopy led to a 25% reduction in the incidence of CRC and a 31% reduction in CRC mortality rate compared with no screening, after a median follow-up of 11.2 years.[11] These large-scale RCTs revealed that the clinical benefit in terms of long-term outcomes was due to treatment for precancerous and early-stage tumours in people who participate in systematic CRC screening programmes.[5–13]

With respect to the cost of CRC screening, there are definite differences among various screening methods for CRC. Some studies have estimated the cost-effectiveness (cost per year of life saved) of a screening test for CRC compared with no screening and with other screening tests.[16–18] Other studies reported that screening for CRC was cost saving, since the cost of cancer treatment, especially that of chemotherapy for advanced CRC, has been increasing.[19] In the USA, as of 2012, 65.1% of adults aged 50–75 years were up-to-date with CRC screening, while 27.7% had never been screened.[26] The percentage of the population that had undergone recommended CRC screening increased from 52.3% in 2002 to 65.4% in 2010,[27] and it seems to have plateaued since then. Reportedly, the spread of screening has contributed to reducing the incidence and mortality of CRC in the USA.[27]

In conclusion, although this study was a retrospective analysis and the sample size was small, we showed that asymptomatic CRC patients had superior short-term perioperative outcomes, as well as long-term oncological outcomes, mainly owing to the greater opportunity for undergoing minimally invasive surgeries. This study shows that participating in some kind of CRC screening programme will facilitate the diagnosis of CRC in its early stages, while patients are still asymptomatic, leading to better long-term oncological outcomes and cost-effectiveness.

Contributors RI performed all analyses, designed the project and drafted the manuscript. TN designed the project, secured the funding and drafted the manuscript. AW, TY, YM, YK, HK and YU provided clinicopathological data and assisted with the interpretation of the data. TF provided

clinicopathological data, assisted with the interpretation of the data and revised the manuscript. All authors read and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Institutional Review Board of Okayama University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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