# Recurrence risk analysis for stage II and III colorectal cancer, and the implications of diabetes mellitus as a risk factor for the recurrence of stage III colorectal cancer

NAOYA KIMURA[1], MASATSUGU HIRAKI[1], SHUNSUKE FURUKAWA[1], KEIICHIRO OKUYAMA[1], NAOHIKO KOHYA[1], MASASHI SAKAI[1], ATSUSHI KAWAGUCHI[2], AKASHI IKUBO[1] and RYUICHIRO SAMEJIMA[1]

[1]Department of Surgery, Japanese Red Cross Society Karatsu Red Cross Hospital, Karatsu, Saga 847-8588, Japan; [2]Education and Research Center for Community Medicine, Saga University Faculty of Medicine, Saga, Saga 849-8501, Japan

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**Abstract.** The present study investigated the risk factors for recurrence in patients with stage II-III colorectal cancer (CRC) who underwent colorectal surgery. Data from 232 patients with stage II and III CRC who underwent primary tumor resection were retrospectively analyzed. Univariate and multivariate analyses were performed to determine the risk factors for recurrence. The overall recurrence rate was 21.6% (n=50/232). Univariate Cox regression analysis identified diabetes mellitus (DM) (P=0.032) as a risk factor for recurrence. In addition, multivariate Cox regression analysis showed that DM was an independent risk factor for recurrence-free survival (RFS) (hazard ratio 2.40, P=0.016). The RFS curve obtained using the Kaplan-Meier method indicated that in patients with stage III colon cancer, the non-DM group demonstrated a significantly longer RFS than the DM group (P=0.012). In conclusion, the present study demonstrated that DM may be an independent risk factor for recurrence in patients undergoing curative resection for stage III CRC. Consequently, better postoperative therapy and careful monitoring might be required, especially in patients with stage III CRC and preoperative DM.

*Correspondence to:* Dr Masatsugu Hiraki, Department of Surgery, Japanese Red Cross Society Karatsu Red Cross Hospital, 2430 Watada, Karatsu, Saga 847-8588, Japan
E-mail: masatsuguhiraki@hotmail.com

*Abbreviations:* CRC, colorectal cancer; DM, diabetes mellitus; UICC, Union for International Cancer Control; TNM, Tumor, Node, Metastasis; PNI, prognostic nutritional index; RFS, recurrence-free survival; OS, overall survival; CT, computed tomography; CD, Clavien-Dindo; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9

*Key words:* CRC, DM, RFS, OS, magnetic resonance imaging

## Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide and ranks third in terms of mortality (1). Globally, approximately 1.9 million new cases of colorectal cancer were reported in 2020, with approximately 930,000 resulting in death (2). The risk of developing colorectal cancer increases with age, particularly in individuals >50 years of age (3). Risk factors include high consumption of processed meat, low intake of fruits and vegetables, sedentary lifestyle, obesity, smoking, and excessive alcohol consumption (4). The standard treatment for stage II or III CRC includes curative resection followed by postoperative adjuvant chemotherapy, depending on the patient's condition and risk of recurrence (5). While the trend in CRC surgery has shifted from open to laparoscopic surgery, including robotic surgery, over time (6) and standard postoperative chemotherapy has been established, recurrence is still observed in many patients. Therefore, identifying prognostic and recurrent risk factors remains a critical clinical theme.

Previous studies have reported that the postoperative recurrence rate for stage II and III CRC is approximately 8.9-30% (7-9). Considering that recurrence significantly diminishes the quality of life of patients and is associated with reduced survival rates, the clinical significance of identifying risk factors for recurrence in colorectal cancer is substantial. Previous studies have argued the existence of several risk factors for recurrence after primary resection of colorectal cancer. However, changes in various patient backgrounds and treatment factors have been observed. Therefore, it is necessary to reexamine the risk of recurrence in the current historical context.

In this study, we examined the risk factors of recurrence in patients with stage II and III CRC who underwent radical surgical resection. In this study, patients with stage I disease were excluded from the study due to the very few instances of recurrence during the 5-year follow-up period. Therefore, based on the results of this analysis, we focused on diabetes mellitus (DM) as a risk factor for recurrence.

## Materials and methods

*Patients*. A retrospective study was conducted among 232 consecutive patients with stage II or III CRC, according to the seventh edition of the Union for International Cancer Control (UICC)-Tumor, Node, Metastasis (TNM) classification, who underwent curative surgery between January 2013 and July 2019 at the Japanese Red Cross Society Karatsu Red Cross Hospital. All the patients underwent colorectal resection accompanied by lymph node dissection. Patients with comorbid cardiovascular, hepatic, and respiratory diseases were included in the study. However, those deemed unfit for surgery and anesthesia based on preoperative assessments were excluded. Additionally, any patients currently undergoing treatment for malignancies in multiple organs were also excluded from the study. The medical records of all patients were reviewed in detail. In this study, 232 patients were divided into two groups based on the presence of recurrence. The median age of the patients was 71 years and the age range was 29 to 91 years. All patients and their families were informed of the surgical procedure and provided written informed consent. The Medical Ethics Committee of the Japanese Red Cross Society Karatsu Red Cross Hospital reviewed and approved the study design (permission number: 23-I-17-01).

*Assessment*. Short-term outcomes included operation time, perioperative blood transfusion, length of hospital stay, and significant postoperative complications. Preoperative blood samples were collected two weeks before surgery. The definition of DM was based on the following criteria: i) currently undergoing diabetes treatment (e.g., insulin administration or the use of hypoglycemic agents). ii) Patients with a preoperative blood test showing HbA1c ≥6.5%. Patients meeting either or both of these criteria were classified as having DM, and all patients with DM had type 2 diabetes. The prognostic nutritional index (PNI) was determined using admission data and the following formula: 10x serum albumin (g/dl) + 0.005 x total lymphocyte count (10). Performance status, smoking history, alcohol consumption history, cardiovascular disease, respiratory disease, and DM were listed as preoperative factors. Postoperative recurrence and the recurrence-free survival (RFS) and overall survival (OS) were evaluated. Postoperative imaging tests such as contrast-enhanced computed tomography (CT), magnetic resonance imaging, and positron emission tomography-CT were used to confirm recurrence or metastasis. RFS refers to the period from surgery to recurrence and OS refers to the period from surgery to death from any cause. Pathological tumor stage was classified according to the seventh edition of the Union for UICC-TNM classification. Postoperative complications were defined as severe if they required surgical intervention and were classified as ≥3 according to the Clavien-Dindo (CD) classification (11,12).

*Statistical analyses*. Continuous variables were expressed as median and interquartile range, and categorical variables were expressed as numbers. In the univariate analysis, Wilcoxon's rank-sum test was used for continuous variables and Fisher's exact test was used for binary variables. Univariate and multivariate analyses of RFS were performed using Cox regression analysis. Multivariate analysis was performed using a stepwise multiple Cox regression analysis. Variables that showed statistical significance (P<0.1) in the univariate analysis were included. The data are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The Kaplan-Meier method was used to describe the distribution of RFS and OS, and the log-rank test was performed. P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were conducted using JMP software (version 17.0; SAS Institute, Cary, NC, USA).

## Results

*Univariate and multivariate analyses for the determination the factor of recurrence:* all patients were followed up for a median of 5.00 (range: 0.11-9.53) years. During this period, 50 patients (21.6%) experienced recurrences. Patient characteristics and univariate analyses comparing the recurrence and non-recurrence groups are presented in Table I. In the univariate analysis, DM (P=0.032), reduced preoperative PNI (P=0.039), increased neutrophil-to-lymphocyte ratio (NLR) (P=0.025), increased carcinoembryonic antigen (CEA) level (P<0.001), increased cancer antigen 19-9 (CA19-9) level (P<0.001), lymph node metastasis (P<0.001), increased intraoperative bleeding (P=0.023), R1 resection (P<0.001), any complication of CD Grade ≥3 (P=0.040), and an extended postoperative hospital stay (P=0.004) were significantly associated with postoperative recurrence. In the univariate analysis of RFS, using Cox regression analysis, DM (P=0.032), reduced preoperative PNI (P=0.027), increased NLR (P=0.01), increased CEA level (P=0.020), increased CA19-9 level (P<0.001), the presence of preoperative bowel obstruction (P=0.035), lymph node metastasis (P<0.001), R1 resection (P<0.001), and anastomotic leakage of CD Grade ≥3 (P=0.035) were identified as risk factors for recurrence (Table II). In the multivariate Cox regression analysis, DM (HR 2.400, 95% CI 1.175-4.902, P=0.016), increased preoperative CA19-9 levels (HR 1.005, 95% CI 1.002-1.009, P=0.004), lymph node metastasis (HR 3.788, 95% CI 1.617-8.876, P=0.006), and R1 resection (HR 12.403, 95% CI 3.459-44.479, P<0.001) were independent risk factors for recurrence. The characteristics of the patients in the DM and non-DM groups are shown in Table III. The DM group had a significantly higher BMI (P<0.001) and significantly lower PS (P<0.001) than the non-DM group. No statistically significant differences were observed in the other parameters.

*Association of DM with the survival in stage II and III CRC patients who underwent colorectal resection*. To examine the impact of DM on postoperative survival, the postoperative survival periods of diabetic (n=48) and non-diabetic patients (n=184) were compared. In the total number of stage II and III cases (n=232), the RFS was significantly longer in the non-DM group than in the DM group (P=0.029), whereas in the analysis of subgroups, there was no significant difference in the RFS between the groups among stage II patients (P=0.592) (Fig. 1). However, the DM group had significantly worse RFS than the non-DM group in stage III patients (P=0.012). No statistically significant differences were observed in OS between the groups at any stage, regardless of DM (Fig. 2).

Table I. Background of the patients and the results of the univariate analyses.

| Characteristic | Recurrence | | P-value |
|---|---|---|---|
| | Negative (n=182) | Positive (n=50) | |
| Patient factors | | | |
| Sex, male:female | 97:85 | 26:24 | 0.875 |
| Median age, years [IQR] | 71 [64-80] | 72 [66-81] | 0.506 |
| Median body mass index, kg/m$^2$ [IQR] | 22.4 [20.2-24.7] | 22.5 [20.5-24.7] | 0.746 |
| ASA-PS, PS1: PS2, 3 | 33:149 | 8:42 | 0.836 |
| Currently smoking, yes:no | 34:148 | 14:36 | 0.169 |
| Currently drinking alcohol, yes:no | 70:112 | 21:29 | 0.744 |
| Cardiac disease, yes:no | 21:161 | 5:45 | >0.999 |
| Pulmonary disease, yes:no | 23:159 | 9:41 | 0.356 |
| Diabetes mellitus, yes:no | 32:150 | 16:34 | 0.032[a] |
| Median hemoglobin, g/dl [IQR] | 11.6 [9.6-13.3] | 12.2 [10.5-13.3] | 0.265 |
| Median PNI [IQR] | 46.8 [42.1-51.7] | 45.1 [40.3-49.2] | 0.039[a] |
| Median NLR [IQR] | 2.28 [1.65-3.15] | 2.76 [1.97-4.08] | 0.025[a] |
| Median CEA [IQR] | 3.7 [2.2-6.3] | 7.8 [3.5-24.2] | <0.001[a] |
| Median CA19-9 [IQR] | 8.6 [3.4-17.8] | 20.7 [5.9-55.6] | <0.001[a] |
| Preoperative bowel obstruction, yes:no | 25:157 | 13:37 | 0.051 |
| Preoperative chemotherapy, yes:no | 8:174 | 6:44 | 0.085 |
| Tumor factor | | | |
| Tumor location, right:left | 78:104 | 16:34 | 0.195 |
| T category, T0-3:T4 | 76:106 | 20:30 | 0.872 |
| N category, negative:positive | 93:89 | 10:40 | <0.001[a] |
| Median maximum tumor length, mm [IQR] | 50 [40-63] | 51 [40-70] | 0.337 |
| Lymphatic invasion, negative:positive | 41:141 | 13:37 | 0.706 |
| Venous invasion, negative:positive | 26:156 | 6:44 | 0.819 |
| Histological type, tub:por. or sig. | 168:14 | 42:8 | 0.099 |
| Operative factor | | | |
| Surgical procedure, open:laparoscopic | 7:175 | 3:47 | 0.453 |
| Median operative time, min [IQR] | 280 [209-391] | 354 [213-450] | 0.120 |
| Median intraoperative bleeding, ml [IQR] | 33 [10-116] | 79 [10-223] | 0.023[a] |
| Blood transfusion, yes:no | 10:172 | 4:46 | 0.508 |
| Emergency operation, yes:no | 1:181 | 0:50 | >0.999 |
| Additional operative procedure, yes:no | 18:164 | 6:44 | 0.610 |
| Stoma creation, yes:no | 20:162 | 11:39 | 0.059 |
| Median number of dissected lymph nodes, [IQR] | 25 [17-33] | 24 [15-30] | 0.206 |
| Lymph node dissection, D1&2:D3 | 16:166 | 2:48 | 0.376 |
| R1 resection, yes:no | 0:182 | 5:45 | <0.001[a] |
| Postoperative factor | | | |
| Any complication ≥CD3, yes:no | 16:166 | 10:40 | 0.040[a] |
| Infectious complication ≥CD3, yes:no | 8:174 | 5:45 | 0.160 |
| Anastomotic leakage ≥CD3 yes:no | 2:180 | 3:47 | 0.068 |
| Median postoperative stay, days [IQR] | 12 [10-18] | 18 [11-30] | 0.004[a] |
| Postoperative chemotherapy, yes:no | 95:87 | 26:24 | >0.999 |

[a]P<0.05. IQR, interquartile range; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9; CD, Clavien-Dindo; tub., tubular adenocarcinoma; por., poorly differentiated adenocarcinoma; sig., signet-ring cell carcinoma

## Discussion

There have been numerous reports on the risk factors for postoperative recurrence of CRC, and an umbrella review of systematic reviews and meta-analyses of observational studies identified 34 risk factors for recurrence, reporting that factors consistently modeled as risks include venous invasion, lymph node metastasis, stage, elevated CEA levels, and high alkaline

Table II. Univariate and multivariate analysis of recurrence-free survival using the Cox regression analysis.

| | Univariate | | Multivariate | | |
|---|---|---|---|---|---|
| Variable | HR (95% CI) | P-value | HR (95% CI) | P-value | VIF |
| Diabetes mellitus | 1.917 (1.058-3.474) | 0.032[a] | 2.400 (1.175-4.902) | 0.016[a] | 1.410 |
| PNI | 0.961 (0.930-0.997) | 0.027[a] | 0.998 (0.948-1.051) | 0.937 | 2.303 |
| NLR | 1.177 (1.030-1.320) | 0.010[a] | 1.089 (0.908-1.306) | 0.358 | 2.343 |
| CEA | 1.007 (1.000-1.011) | 0.020[a] | 1.001 (0.992-1.010) | 0.839 | 1.656 |
| CA19-9 | 1.005 (1.002-1.007) | <0.001[a] | 1.005 (1.002-1.009) | 0.004[a] | 2.303 |
| Preoperative bowel obstruction | 1.971 (1.047-3.710) | 0.035[a] | 1.580 (0.719-3.048) | 0.287 | 1.213 |
| Preoperative chemotherapy | 2.221 (0.946-5.213) | 0.067 | 1.597 (0.554-4.608) | 0.386 | 1.524 |
| N category | 3.561 (1.781-7.122) | <0.001[a] | 3.788 (1.617-8.876) | 0.006[a] | 1.168 |
| Histological type (por. or sig.) | 1.963 (0.921-4.183) | 0.081 | 0.908 (0.276-2.986) | 0.874 | 2.366 |
| Intraoperative bleeding | 1.000 (0.999-1.001) | 0.052 | 1.001 (0.100-1.002) | 0.064 | 1.551 |
| R1 resection | 13.638 (5.319-34.966) | <0.001[a] | 12.403 (3.459-44.479) | <0.001[a] | 1.802 |
| Infectious complication ≥CD3 | 2.273 (1.136-4.548) | 0.090 | 2.272 (0.492-10.493) | 0.293 | 2.711 |
| Anastomotic leakage ≥CD3 | 3.525 (1.092-11.382) | 0.035[a] | 0.108 (0.009-1.263) | 0.076 | 4.368 |

[a]P<0.05. CI, confidence interval; HR, hazard ratio; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9; CD, Clavien-Dindo; VIF, variance inflation factor; por., poorly differentiated adenocarcinoma; sig., signet-ring cell carcinoma

Table III. Background of characteristics of patients in the DM and non-DM groups.

| | DM | | |
|---|---|---|---|
| Characteristic | Negative (n=182) | Positive (n=50) | P-value |
| Sex, male:female | 98:86 | 25:23 | 0.884 |
| Median age, years [IQR] | 71 [63-80] | 71.5 [66.3-82] | 0.214 |
| Median body mass index, kg/m$^2$ [IQR] | 22.1 [19.5-24.3] | 23.9 [21.9-25.8] | <0.001[a] |
| ASA-PS, PS1:PS2, 3 | 41:183 | 0:48 | <0.001[a] |
| Currently smoking, yes:no | 40:144 | 8:40 | 0.431 |
| Currently drinking alcohol, yes:no | 70:114 | 21:27 | 0.473 |
| Cardiac disease, yes:no | 21:163 | 5:43 | 0.844 |
| Pulmonary disease, yes:no | 24:160 | 8:40 | 0.525 |
| Median hemoglobin, g/dl [IQR] | 11.9 [10.0-13.3] | 11.5 [9.2-13.1] | 0.231 |
| Median PNI, [IQR] | 46.3 [41.6-51.0] | 45.7 [42.9-50.8] | 0.100 |
| Median NLR, [IQR] | 2.30 [1.7-3.5] | 2.68 [2.0-3.8] | 0.132 |
| Median CEA [IQR] | 3.9 [2.2-8.5] | 4.0 [3.1-8.3] | 0.360 |
| Median CA19-9 [IQR] | 9.4 [4.2-23.5] | 10 [3.3-24.9] | 0.911 |
| Preoperative bowel obstruction, yes:no | 33:151 | 5:43 | 0.190 |
| Preoperative chemotherapy, yes:no | 13:171 | 1:47 | 0.150 |

[a]P<0.05. IQR, interquartile range; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9; CD, Clavien-Dindo.

phosphatase values (13). However, in addition to the changing historical background, the patient and treatment contexts have also changed. Therefore, it is important to consider the risk factors for recurrence.

According to previous studies, the 5-year RFS was 79% in the laparoscopic surgery group and 80% in the open surgery group (14). Considering the ratio of patients with Stage II to Stage III in this study (103 stage II vs. 129 stage III), a recurrence rate of around 20% for the overall stage II-III population is consistent with the data reported by other institutions. In our study, DM, increased CA19-9 level, lymph node metastasis, and R1 resection were independent risk factors for recurrence. Previous studies have also identified preoperative CA19-9 levels, lymph node metastasis, and R1 resection as

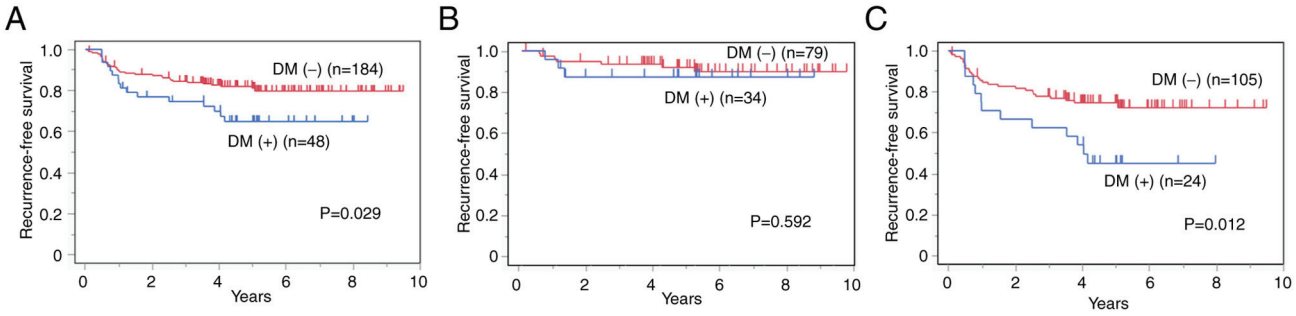


Figure 1. Recurrence-free survival curves of DM and non-DM groups. (A) In patients with stage II and III CRC. (B) In patients with stage II CRC. (C) In patients with stage III CRC. CRC, colorectal cancer; DM, diabetes mellitus.

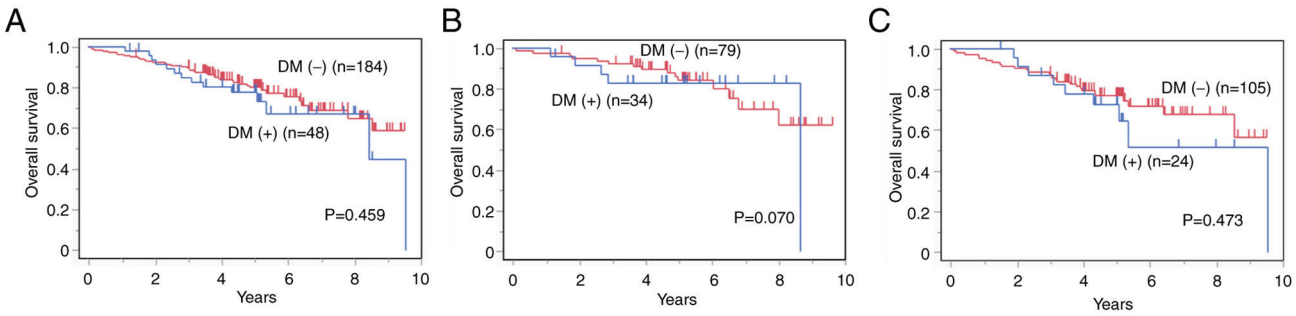


Figure 2. Overall survival curves of DM and non-DM groups. (A) In patients with stage II and III CRC. (B) In patients with stage II CRC. (C) In patients with stage III CRC. CRC, colorectal cancer; DM, diabetes mellitus.

risk factors for recurrence, which is consistent with previous reports (15-17). Patients with elevated preoperative CEA and CA19-9 levels have a higher risk of recurrence. Notably, the recurrence rate was significantly higher when both markers were elevated. Patients with preoperative CEA and CA19-9 levels of ≥200 have an exceedingly high risk of recurrence (18). Additionally, if the levels of these tumor markers do not normalize postoperatively, they are considered to be predictive of recurrence (19). Although our study lacked postoperative tumor marker data, our findings are largely consistent with those of previous studies. However, the impact of diabetes on the prognosis of patients with CRC remains largely unclear.

We identified DM as an independent risk factor for recurrence in patients with stage II and III colorectal cancer. Interestingly, a subgroup analysis demonstrated that patients with DM had a significantly poorer RFS than those without DM only in cases of stage III disease. Previous systematic reviews and meta-analyses have reported that DM patients with stage I-III disease have an increased risk of postoperative complications and a higher rate of cancer recurrence over a five-year period than non-DM patients (20). However, there is no mention of an individualized analysis according to cancer stage or its significance.

The impact of DM on the prognosis of patients with CRC remains unclear. DM is a chronic metabolic disease affecting major metabolic pathways and has been linked to the progression and survival of various cancers, including esophageal (20), liver (21), pancreatic (22), gallbladder (23), breast (24), and lung cancers (25). DM is also considered an independent risk factor (26). A meta-analysis of 2,593,955 CRC patients found that diabetic patients had a hazard ratio of 1.30 and a mortality rate of 1.26 compared to non-diabetics (27). A previous study reported that approximately 80-90% of diabetic patients are concurrently obese (28), and chronic hyperinsulinemia and hyperglycemia contribute to the accumulation of visceral fat (29). Obesity and fat storage are associated with a chronic inflammatory state, which results in the active production of various inflammatory factors, adipokines, free fatty acids, and extracellular matrix, contributing to the construction of a tumor-supporting microenvironment (30). In addition, the production of these inflammatory cytokines due to obesity has been shown to induces insulin resistance, potentially intensifying the tumor-promoting effects of hyperinsulinemia (31). Although this study did not identify obesity as a recurrent risk factor, the relationship between DM, particularly that characterized by insulin resistance, and tumor recurrence and proliferation cannot be negated from this perspective. Therefore, it is possible that the microenvironment in the body due to DM contributed to cancer recurrence in this study. In this study, RFS in stage III patients with DM was worse than that in stage III patients but not in stage II. We speculated that a lower stage of CRC might contribute less to recurrence. However, further studies are required to clarify the relationship between recurrence and DM.

In this study, no statistically significant difference was observed in OS between the DM and non-DM groups in either stage II or III disease. In previously reported cohort studies of patients with high-risk stage II and III colorectal cancer, in a 5-year period, the group with DM showed a significantly lower RFS (48 vs. 59% non-DM; P<0.0001)

and OS (57% DM vs. 66% non-DM; P<0.0001) than the non-DM group, which differs from our findings (32). In our study, an extension of RFS was observed solely in stage III, while it was not observed in stage II. In addition, a statistically significant extension of the overall survival period was not observed in either stage II or III cases. This may be due to the advent of better postoperative therapies or differences in the historical background owing to the use of potent chemotherapy at the time of recurrence. Previous reports have indicated that some hypoglycemic agents may enhance the efficacy of chemotherapy in cancers such as breast, prostate, and colorectal cancers (33,34). It is also possible that a specific combination of chemotherapy and hypoglycemic agents influenced RFS without affecting OS in patients with or without diabetes. However, owing to the lack of detailed data on postoperative diabetic therapy in the present study, it is not possible to discuss this aspect. Therefore, further research on postoperative regimens and diabetes treatments is required to clarify the relationship between DM, RFS, and OS.

Several limitations of the present study warrant mention. This retrospective study was conducted at a single institution. First, the difficulty in acquiring a wide range of patients from diverse backgrounds could lead to a selection bias. Additionally, the possibility of regional or facility-specific patient characteristics cannot be ruled out. Second, the proportion of patients with DM was relatively small, which may have reduced the statistical significance of our results. Therefore, the lack of statistically significant differences in overall survival between the non-DM and DM groups may be due to insufficient statistical power. Third, the study period was relatively long, lasting 6.5 years. Advances in surgical techniques during this period and the transition from open to laparoscopic surgery, which reduces invasiveness, might have affected postoperative complications and the timing of chemotherapy introduction, potentially leading to an underestimated or overestimated impact on the recurrence rate of DM. Fourth, the severity of diabetes was not stratified, and detailed data on diabetes treatment were lacking. We cannot comment on the correlation between diabetes severity and recurrence frequency, or on treatments that may influence recurrence. Regarding the DM criteria of this study, it is possible that some untreated DM patients with HbA1c <6.5% were included in the non-DM group. This factor could have potentially influenced the final results. Further studies are needed to clarify the impact of DM on the risk of recurrence.

In conclusion, while DM does not affect OS, it may be a risk factor for the recurrence of stage III colorectal cancer following radical intestinal resection. For patients with stage III CRC who have undergone resection and have diabetes, it is necessary to maintain proper glycemic control and lifestyle modifications to prevent obesity.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

NKi and MH designed the study. SF, MH, NKi, KO, NKo, MS, AI and RS collected the data. NKi, MH and SF confirmed the authenticity of all the raw data. NKi and MH analyzed the data. AK supervised the statistical analysis. NKi and MH interpreted the results and wrote the manuscript. All authors edited the manuscript. RS supervised the study and approved the final manuscript. All authors have read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

The Medical Ethics Committee of the Japanese Red Cross Society Karatsu Red Cross Hospital reviewed and approved the study design (permission number: 23-I-17-01). The requirement of informed consent for the present study from all patients was waived due to the retrospective design. Patients were informed about the study using opt-out methods, and all patients chose to participate; none declined participation.

**Patient consent for publication**

Patient consent for publication was obtained through opt-out methods.

**Competing interests**

The authors declare that they have no competing interests.

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