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# Prognostic Impact of Diabetes Mellitus on Colorectal Cancer

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## Abstract

**Background:** Diabetes mellitus (DM) is suggested to be associated with colorectal cancer (CRC); however, the direct relationship between DM and CRC has not been proven.

**Objective:** The aim of this study is to clarify oncological behavior of CRC with DM.

**Methods:** This study is a retrospective cohort study. We investigated 1216 patients with curatively resected CRC. Clinicopathological factors and prognosis were compared between the patients with and without DM.

**Results:** DM was observed in 34% of the patients. The patients with DM were significantly older, were predominantly males, had larger tumors, and died more frequently of causes other than CRC than those without DM. While overall survival (OS) was significantly inferior in the patients with DM than in those without (83% vs. 88%, p=0.01), there was no difference in cancer-specific survival (CSS) between the two groups (91% vs. 91%, p=0.6). The examination of survival at each cancer stage showed that CSS of the patients with DM tended to be superior in stage II cancer (97% vs. 93%, p=0.07) and was worse in stage IV cancer (54% vs. 70%, p=0.05).

**Conclusions:** OS was worse in the CRC patients with DM who more often died of causes other than CRC, and thus, DM did not affect CSS as a whole. However, with the progression of CRC, DM appeared to worsen CSS. It is unclear whether this is attributed to differences in malignancy or in treatment; this should be further examined.

**Keywords:** Colorectal cancer; Diabetes mellitus; Surgery; Prognosis

## Introduction

Many epidemiological studies have reported a relationship between diabetes mellitus (DM) and cancer, some of which suggested that DM is associated with colorectal cancer (CRC) [1-8]. Some case-control studies revealed that abnormal glucose intolerance or DM is more common among patients with CRC than among controls [1-3], and some cohort studies showed that a history of DM or insulin resistance increases the risk of developing CRC [4-8]. However, most of these studies showed that there is a relationship between DM and the onset of CRC only. Whether DM is directly related to cancer [9,10], whether DM is an indicator of potential factors that alter cancer risk [11-13], or whether the association between DM and cancer is indirect via common risk factors [14-16], remain unclear [17]. Furthermore, prognosis has not been fully examined, with some reports describing short-term postoperative mortality [18-20].

Therefore, in this study, we aimed to examine the clinicopathological characteristics and postoperative prognosis of patients with curatively resected CRC and DM and to clarify oncological behavior of CRC with DM.

## Patients and Methods

### Patient population

This was a retrospective study of 1216 patients who underwent elective and curative surgery for primary CRC in the University of Tokyo Hospital between January 2000 and December 2009. Patients with curatively resected distant metastases were also enrolled. In patients with multiple synchronous CRCs, only the largest lesion was considered. The mean follow-up period from the date of surgery to the date of death or to the last visit to the hospital was 74 ± 39 months. The study was performed with the approval of the ethics committee of the University of Tokyo Hospital.

### Definition of diabetes mellitus

We used all blood sample data recorded in medical charts of our hospital. In accordance with the Japanese diabetes diagnostic criteria [21], DM was defined as having a fasting blood glucose (FBG) level of 126 mg/dl (7 mmol/L) or higher on at least two occasions or having an FBG level of 126 mg/dl (7 mmol/L) or higher and an hemoglobin A1c (HbA1c) (NGSP) level of 6.5% or higher. Patients whose past data satisfied these criteria and those receiving DM treatment were regarded as patients with a diagnosis of DM. Preoperative blood tests were performed without receiving intravenous nutrition within approximately one month before colorectal surgery. Because some patients had a blood sample drawn only once and had only one set of data, a strict diagnosis of DM could not be made for such patients.

However, the patients with an FBG level of 126 mg/dl (7 mmol/L) or higher or an HbA1c level of 6.5% or higher were very strongly suspected of having DM, and we diagnosed them as having DM. Therefore, we defined the patients with an FBG level of 126 mg/dl (7 mmol/L) or higher, an HbA1c level of 6.5% or higher, or a diagnosis of DM as having DM.

### Data collection

Clinical variables such as sex, age, blood sample data including FBG and HbA1c levels, medical history, histopathological parameters related to the tumor, presence or absence of distant metastases, receiving preoperative (chemo) radiation therapy or not, date of surgery, surgical procedure, presence or absence of postoperative recurrence, date of death or the last visit to the hospital, and cause of death were retrospectively obtained from the prospectively generated medical records. The pathological description of CRC was essentially based on the TNM classification, seventh edition [22].

### Statistical analysis

Statistical analyses were performed using SPSS version 16.0 (IBM, Chicago, USA). We compared clinicopathological factors between the patients with and without DM by chi-square and paired t tests. The prognoses of the patients were compared by the analysis of overall survival (OS) and cancer-specific survival (CSS). Survival curves were created using the Kaplan–Meier method and were compared using the log-rank test. A multivariate analysis for factors associated with each type of survival was performed using Cox proportional hazard analysis of items with p-values <0.1 generated by univariate analysis. In analyses other than the univariate analysis above, p-values <0.05 were considered statistically significant.

## Results

### Characteristics of CRC patients

The clinicopathological characteristics of the 1216 CRC patients included in our study are summarized in Table 1.

The patients were predominantly males (63%), with a mean age of 66 years (range, 27–94 years). The mean FBG and HbA1c levels were 115 mg/dl (6.4 mmol/L) and 5.8%, respectively. The majority of tumors were located in the rectum (42%), of which 29% received neoadjuvant (chemo) radiation therapy. The mean tumor diameter was 41 mm. Histologically, well or moderately differentiated adenocarcinomas accounted for 94% of the patients, with lesions extending through the muscularis propria in 62%. Regional lymph nodes were positive for metastases in 34% of the patients, and distant metastases were observed in 8%. Postoperative recurrence was observed in 25% of the patients, and death during the follow-up period in 16%. The cause of death was related to CRC in 61% of the patients.

### Characteristics of CRC patients with DM

Patients with DM (n=416), one of whom suffered from insulin dependent DM (IDDM) and 415 from non-insulin dependent DM (NIDDM), comprised 34% of the total number of patients in this study, and those without DM (n=800) comprised 66%. The mean period from the diagnosis of DM to the surgery was 41 ± 78 months (range, 1-564 months). The halves of patients with DM were diagnosed by preoperative blood tests within two months before the surgery. The clinicopathological characteristics of CRC were compared between the patients with and without DM (Table 1). The mean age of the patients with DM was 68 years, which was significantly higher than that of the patients without DM (64 years; $p < 0.0001$). The proportion of male patients was significantly higher in the group with DM than in that without DM (73% vs. 58%, $p < 0.0001$). The mean FBG and HbA1c levels of the patients with DM were 145 mg/dl (8.1 mmol/L) and 6.5%, respectively, which were significantly higher than those in the patients without DM (100 mg/dl (5.6 mmol/L) and 5.5%, both $p < 0.0001$). The most frequent tumor location was the rectum in both groups, while in the remaining patients, the tumor tended to be more frequently in the proximal colon, defined as colon proximal to the splenic flexure, in the group with DM than in that without DM (49% vs. 43%, p=0.09). The patients with DM had significantly larger tumors than those without DM (43 mm vs. 39 mm in diameter, p=0.02). Deeper invasion by the lesion was observed in the group with DM than in that without DM, although the difference was not statistically significant (p=0.1). Regarding macroscopic tumor type, more patients with DM tended to have invasive type cancer (p=0.08, data not shown). The patients with DM died of other causes significantly more often than CRC recurrence, while in those without DM the most frequent cause of death was CRC recurrence (p=0.02). Other clinicopathological factors were also compared; however, no significant differences were observed.

| | ALL (n=1216) | DM+ (n=416) | DM- (n=800) | p |
|---|---|---|---|---|
| **Age, mean ± SD (years)** | 66 ± 11 | 68 ± 10 | 64 ± 11 | <0.001 |
| **Sex, n (%)** | | | | <0.001 |
| Male | 763 (63) | 302 (73) | 461 (58) | |
| Female | 453 (37) | 114 (27) | 339 (42) | |
| **FBG, mean ± SD (mg/dl)** | 115 ± 35 | 145 ± 44 | 100 ± 12 | <0.001 |
| **FBG, mean ± SD (mmol/L)** | 6.4 ± 1.9 | 8.1 ± 2.4 | 5.6 ± 0.7 | <0.001 |
| **HbA1c, mean ± SD (%)** | 5.8 ± 0.9 | 6.5 ± 1.2 | 5.5 ± 0.4 | <0.001 |
| **Location of tumor, n (%)** | | | | 0.5 |
| Colon | 703 (58) | 246 (59) | 457 (57) | 0.09 |

| | | | | |
|---|---|---|---|---|
| Proximal colon[a] | 315 (45) | 121 (49) | 194 (42) | |
| Distal colon[a] | 388 (55) | 125 (51) | 263 (58) | |
| Rectum | 513 (42) | 170 (41) | 343 (43) | |
| **Maximum tumor diameter, mean ± SD (mm)** | 41 ± 23 | 43 ± 23 | 39 ± 23 | 0.02 |
| **Tumor differentiation, n (%)** | | | | 0.2 |
| Differentiated | 1148 (94) | 397 (95) | 751 (94) | |
| Undifferentiated | 68 (6) | 19 (5) | 49 (6) | |
| **Depth, n (%)** | | | | 0.1 |
| T0 or Tis[b] | 50 (4) | 18 (4) | 32 (4) | |
| T1 | 206 (17) | 57 (14) | 149 (19) | |
| T2 | 207 (17) | 78 (19) | 129 (16) | |
| T3 | 566 (47) | 205 (49) | 361 (45) | |
| T4 | 187 (15) | 58 (14) | 129 (16) | |
| **Lymphatic invasion, n (%)** | | | | 0.7 |
| - | 906 (75) | 314 (75) | 592 (74) | |
| + | 305 (25) | 102 (25) | 203 (26) | |
| **Venous invasion, n (%)** | | | | 0.3 |
| - | 505 (42) | 181 (44) | 324 (41) | |
| + | 707 (58) | 235 (56) | 472 (59) | |
| **Regional lymph node metastasis, n (%)** | | | | 0.3 |
| - | 803 (66) | 284 (68) | 519 (65) | |
| + | 411 (34) | 132 (32) | 279 (35) | |
| **Distant metastasis, n (%)** | | | | 0.6 |
| - | 1117 (92) | 380 (91) | 737 (92) | |
| + | 99 (8) | 36 (9) | 63 (8) | |
| **UICC stage, n (%)** | | | | 0.5 |
| 0[b] | 48 (4) | 17 (4) | 31 (4) | |
| I | 349 (29) | 113 (27) | 236 (30) | |
| II | 376 (31) | 141 (34) | 235 (29) | |
| III | 344 (28) | 109 (26) | 235 (29) | |
| IV | 99 (8) | 36 (9) | 63 (8) | |
| **Preoperative RT or CRT for rectal cancer,c n (%)** | 149 (29) | 52 (30) | 97 (28) | 0.6 |
| **Recurrence, n (%)** | 302 (25) | 102 (25) | 200 (25) | 0.9 |
| **Follow-up period, mean ± SD (days)** | 74 ± 39 | 71 ± 39 | 75 ± 39 | 0.09 |
| **Cause of death, n (%)** | | | | 0.02 |
| CRC recurrence | 122 (61) | 43 (52) | 79 (68) | |

| | | | | |
|---|---|---|---|---|
| Other than CRC recurrence | 63 (32) | 35 (42) | 28 (24) | |
| Other cancers than CRC[d] | 30 (48) | 14 (40) | 16 (57) | |
| Pneumonia[d] | 11 (17) | 5 (14) | 6 (21) | |
| Heart disease[d] | 4 (6) | 4 (11) | 0 (0) | |
| Cerebrovascular disease[d] | 3 (5) | 2 (6) | 1 (4) | |
| Others[d] | 15 (24) | 10 (29) | 5 (18) | |
| Unknown | 15 (8) | 5 (6) | 10 (9) | |

CRC: Colorectal Cancer; DM: Diabetes Mellitus; SD: Standard Deviation; FBG: Fasting Blood Glucose; HbA1c: Hemoglobin A1c; RT: Radiation Therapy; CRT: Chemoradiatiotherapy; CR: Complete Response

[a]The denominator was the total number of patients with colonic cancer.

[b]Including cases of pathological CR after preoperative (chemo) radiation for primary cancer.

[c]The denominator was the total number of patients with rectal cancer.

[d]The denominator was the total number of patients who died of other causes than CRC recurrence.

**Table 1:** Clinical and pathological profiles of CRC patients with DM.

### Long-term outcomes

We analyzed OS and CSS of the CRC patients with and without DM. The mean follow-up period was 71 ± 39 months for the patients with DM and 75 ± 39 months for those without DM, with the former tending to be shorter (p=0.09, Table 1). Figure 1 shows the OS curves. The 5-year OS of the CRC patients with DM was 83%, which was worse than that of those without DM (88%) (p=0.02). Throughout the follow-up period, OS of the CRC patients with DM was significantly inferior to that of the patients without DM (p=0.01). Furthermore, we investigated OS of the patients at each cancer stage and found that OS of the patients with DM was significantly inferior at stages 0-Iand stage IV (92% vs. 97%, p=0.009 and 52% vs. 69%, p=0.04, respectively). To verify that DM was truly associated with long-term outcome, a multivariate analysis was performed (Table 2), revealing that DM was an independent prognostic factor.

Other factors such as age, tumor size, tumor differentiation, tumor invasion depth, venous invasion, regional lymph node metastasis, and distant metastasis were also independent prognostic factors. On the other hand, there was no significant difference in CSS between the patients with DM and those without DM (p=0.6, Figure 2). Both the 5-year CSS of the CRC patients with and without DM were 91%. However, the examination of each cancer stage showed that the prognosis of the patients with DM tended to be superior at stage II (97% vs.93%, p=0.07) and significantly inferior at stage IV (54% vs. 70%, p=0.05). A multivariate analysis to verify the factors associated with CSS at stage IV cancer revealed that DM was an independent prognostic factor (Table 3). Tumor differentiation and lymphatic invasion were also found to be prognostic factors.

## Discussion

In this study, we compared clinicopathological characteristics, postoperative OS, and CSS of the CRC patients with and without DM based on a database of patients who underwent curative surgery over the past 10 years in our department. The CRC patients with DM were significantly older and more likely to be males and had larger tumors diameter compared with those without DM. Furthermore, in general, DM was associated with worse OS but had no effect on CSS. The examination of each cancer stage showed that CSS tended to be superior in the stage II patients with DM but was significantly worse in the stage IV patients; in other words, DM negatively affected CSS in more advanced cancer patients.

Studies have also reported that the CRC patients with DM are older and more likely to be males [2,6]; however, we were unable to find any reports on tumor size. Although not shown in our results, we performed a sub analysis for the CRC patients with DM to examine whether there was a difference in tumor diameter between a good blood glucose control group with normal FBG and HbA1c levels on preoperative blood data (n=65) and a poor control group (n=340). We found that in the good blood glucose control group, the tumor diameter was 38 mm, which was smaller than the diameter of 44 mm observed in the poor control group (p=0.05). Hence, the patients with DM and poor blood glucose control had larger tumors. CRC cells tend to exhibit anaerobic metabolism and therefore require glucose for cell growth. In hyperglycemia, energy sources are abundant, and thus, a hyperglycemic environment is assumed to be beneficial for cell growth. Some reports have suggested that hyperglycemia contributes to the onset of CRC [9,23]; however, it is possible that it may affect tumor growth only after onset. Furthermore, on comparing tumor site in colonic cancer only, we found that the tumor in the patients with DM tended to be located more often in the proximal colon. Another article reported similar findings [24]. It was reported in a study that colonic polyps, which are precancerous, are more often found in the proximal colon in patients with DM [25]. Moreover, underlying mechanisms related to DNA have been explored [26]; however, the details remain unclear, and further research is anticipated.

| | Univariate analysis | Multivariate analysis | |
|---|---|---|---|
| | p | HR (95% CI) | p |
| **Age (years)** | 0.04 | | 0.02 |
| ≤ 65 | | 1 | |
| ≥ 66 | | 1.40 (1.05-1.88) | |
| **Sex** | 1 | | |
| Male | | | |
| Female | | | |
| **DM** | 0.01 | | 0.008 |
| - | | 1 | |
| + | | 1.48 (1.11-1.98) | |
| **Location of tumor** | 0.8 | | |
| Colon | | | |
| Rectum | | | |
| **Maximum tumor diameter (mm)** | <0.001 | | 0.04 |
| < 40 | | 1 | |
| ≥ 40 | | 1.41(1.02-1.96) | |
| **Tumor differentiation** | <0.001 | | 0.004 |
| Differentiated | | 0.50 (0.31-0.80) | |
| Undifferentiated | | 1 | |
| **Depth** | <0.001 | | 0.008 |
| T0-2 | | 1 | |
| T3,4 | | 1.78 (1.17-2.73) | |
| **Lymphatic invasion** | <0.001 | | 0.1 |
| - | | 1 | |
| + | | 1.30 (0.95-1.79) | |
| **Venous invasion** | <0.001 | | 0.02 |
| - | | 1 | |
| + | | 1.51 (1.08-2.12) | |
| **Regional lymph node metastasis** | <0.001 | | 0.01 |
| - | | 1 | |
| + | | 1.50 (1.01-2.06) | |
| **Distant metastasis** | <0.001 | | <0.001 |
| - | | 1 | |
| + | | 2.20 (1.49-3.26) | |

HR: Hazard Ratio; CI: Confidence Interval; DM: Diabetes Mellitus

**Table 2:** Multivariate analysis of factors involved in overall survival at all stages.

| | Univariate analysis | Multivariate analysis | |
|---|---|---|---|
| | *p* | HR (95% CI) | *p* |
| **Age (years)** | 0.9 | | |
| ≤ 65 | | | |
| ≥ 66 | | | |
| **Sex** | 0.5 | | |
| Male | | | |
| Female | | | |
| **DM** | 0.05 | | 0.002 |
| - | | 1 | |
| + | | 3.13 (1.50-6.55) | |
| **Location of tumor** | 0.4 | | |
| Colon | | | |
| Rectum | | | |
| **Maximum tumor diameter (mm)** | 0.6 | | |
| < 40 | | | |
| ≥ 40 | | | |
| **Tumor differentiation** | <0.001 | | <0.001 |
| Differentiated | | 0.07 (0.02-0.18) | |
| Undifferentiated | | 1 | |
| **Depth** | 0.2 | | |
| T0-2 | | | |
| T3-4 | | | |
| **Lymphatic invasion** | 0.06 | | 0.02 |
| - | | 1 | |
| + | | 2.30 (1.17-4.53) | |
| **Venous invasion** | 0.2 | | |
| - | | | |
| + | | | |
| **Regional lymph node metastasis** | 0.3 | | |
| - | | | |
| + | | | |

HR: Hazard Ratio; CI: Confidence Interval; DM: Diabetes Mellitus

**Table 3:** Multivariate analysis of factors involved in cancer-specific survival at stage IV.

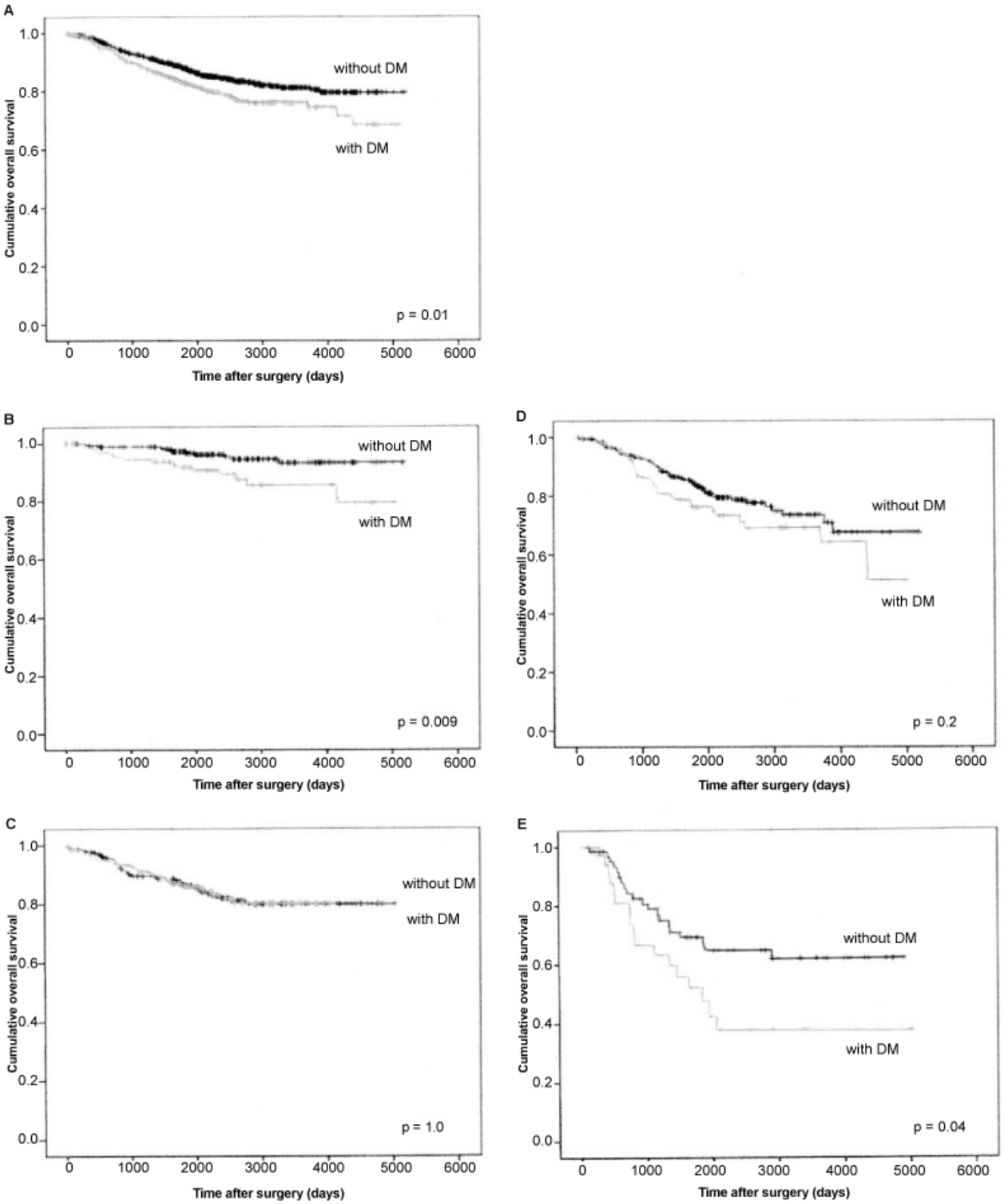


**Figure 1:** Overall survival curves of CRC patients with and without DM. (A: all, B: stages 0-I, C: stage II, D: stage III, E: stage IV).

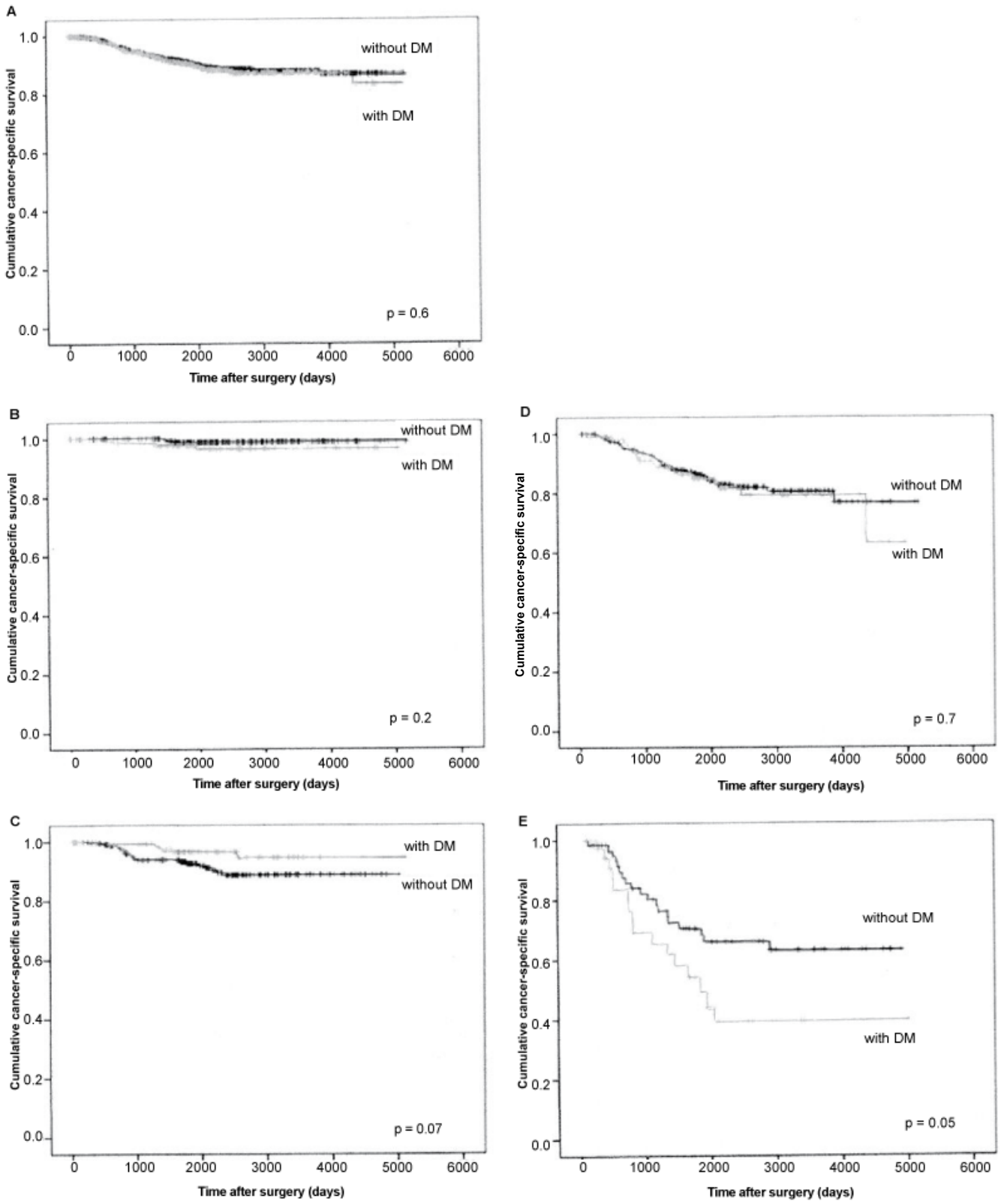


**Figure 2:** Cancer-specific survival curves of CRC patients with and without DM. (A: all, B: stages 0-I, C: stage II, D: stage III, E: stage IV).

The analysis of the survival of all patients revealed that the patients with DM had significantly inferior OS but that there was no difference in CSS. In other words, inferior OS could be attributed to causes of death other than cancer, such as concurrent DM or complications of DM. This reasoning is supported by the fact that significantly more patients with DM died of causes unrelated to CRC. It was mentioned in another report that while there is a significant difference in 5-year survival following curative resection, there is no difference in CSS, which is attributed to advanced age and high frequency of heart disease [27]. We can expect that the treatment of DM and its complications improve the OS of CRC patients, as well as early detection and treatment of CRC recurrence. Our multivariate analysis aiming to verify the factors adversely affecting survival revealed that DM was an independent prognostic factor. In addition, old age, poorly differentiated cancer, large tumor, tumor with deep invasion, lymph duct metastasis, regional lymph node metastasis, and distant metastasis were also independent adverse prognostic factors. DM is the leading cause of death worldwide [28], and it has been reported that in patients with poorly differentiated cancer, prognosis is poor [29].

The examination of each cancer stage showed that the stage 0-I patients with DM had significantly inferior OS. However, cancer-related death is unlikely at the early stage, and in fact, there was no significant difference in CSS between stage 0-I patients with and without DM. Therefore, we believe that concurrent DM or complications of DM greatly affected OS in stage 0-I cancer. Given that the effect of concurrent DM or complications of DM in stage II cancer were the same as those in stage 0-I cancer, we expected that OS in the patients with stage II cancer would also become worse; however, no significant difference was observed, which is thought to be because of the good CSS. The stage II patients with DM tended to have superior CSS, which is thought to reflect the specificity of the tumor because stage II cancer has no lymph node metastasis, and unless there is recurrence, adjuvant chemotherapy is not administered to majority of the patients. In other words, it is possible that CRC with DM may be less aggressive at the early stage; however, further verification is needed. In contrast, CSS was significantly worse in the stage IV patients with DM. This suggests at least two possibilities. First, it is possible that CRC with DM was more aggressive in more advanced stages. Second, it is possible that concurrent DM caused a difference in postoperative treatment and the outcomes of such treatment. In more advanced CRC, postoperative adjuvant chemotherapy is often administered, and a high incidence of recurrence is seen, after which treatment with anticancer agents is often administered. DM complications may impede the proactive administration of anticancer agents or the effect of anticancer agents. The good control of DM and its complications might enable more effective treatments for CRC and improve the CSS of the patients. Our multivariate analysis revealed that DM was an independent prognostic factor. Poor differentiation and lymphatic invasion were also significant factors of poor prognosis. Recent reports indicated that specific DM medications affect the risk of developing cancer. For example, it has been suggested that metformin reduces the risk of cancer [30], whereas insulin preparations increase the risk of cancer [31]. The substantial duration of DM was unclear, because many patients were diagnosed with DM by preoperative blood tests just before the surgery.

In our study, some other information pertaining to DM was insufficient, such as the state of postoperative blood glucose control and which DM treatments were used, and therefore, there were limitations to our study. Furthermore, a fundamental limitation in this field of research includes the difficulty in specifying the time of cancer onset, and therefore, in the case of concurrent DM and CRC, it is unclear which developed first. Many studies take the stance that DM is the underlying cause; however, the possibility that cancer influences DM cannot be denied. Other limitations include the retrospective nature of this study, and findings in this study must be confirmed in future prospective studies.

In conclusion, the CRC patients with DM were significantly older, were more likely to be males, and had larger tumors than those without DM. Furthermore, DM was an independent prognostic factor of CRC. In the patients with DM compared with those without, OS was significantly worse, whereas CSS did not differ, and based on the fact that the cause of death was significantly more often unrelated to CRC, we assume that in CRC with DM, OS was reduced as a result of DM complications. With advancing cancer stage, the adverse effect of DM on CSS tended to increase; however, it is unclear whether this could be attributed to differences in malignancy or in the choice of treatment; therefore, this should be examined further.

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