research article

Long term survival in 200 patients with advanced stage of colorectal carcinoma and diabetes mellitus – a single institution experience

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Background. Diabetes mellitus (DM) and DM related comorbidities may initiate difficulties during cancer specific treatment and may have an impact on cancer management and outcome. The aim of our study was to find out if DM in patients with advanced colorectal carcinoma (CRC) is associated with cancer-specific or overall survival.

Patients and methods. This study included 200 consecutive patients (131 males, 69 females, mean age 63 years) with elective CRC surgery at the Institute of Oncology Ljubljana and DM was found in 39 (19.5%) of them. Even 64% of patients had Stage 3 or 4 disease, so neo-adjuvant chemotherapy (CTX) and/or radiotherapy (RT) were carried out in 59% of cases. Data about gender, age, body mass index, presence of DM, American Society of Anesthesiologists (ASA) physical status score, stage of disease and postoperative complications were collected prospectively. Cancer-specific survival and overall survival were compared by log-rank test.

Results. Patients with DM had a higher ASA score, BMI, the illness marker, rate of massive bleeding, blood transfusion and longer hospital stay than those without DM. The mean follow-up period was 4.75 years. All causes mortality in patients with DM and without DM was 23% and 27%, respectively. Three-year cancer-specific survival in patients with DM and without DM was 85% and 89%, respectively (p = 0.68). Three-year overall survival in patients with DM and without DM was 82% and 84%, respectively (p = 0.63).

Conclusions. The presence of DM was not associated with tumor stage, disease-specific survival or overall survival in patients with advanced CRC.

Key words: colorectal carcinoma, diabetes mellitus, surgery, survival

Introduction

Diabetes mellitus (DM) is known to be an independent risk factor for the development of colorectal cancer (CRC).[1,2] The risk of colorectal cancer was estimated to be 27% higher in patients with type 2 DM than in non-diabetic controls.[3] However, it is unclear if the presence of diabetes in patients with CRC is associated with the cancer-specific survival of patients after cancer diagnosis.[4] Some authors found that patients with CRC and diabetes are at greater risk of all-cause and cancer-specific mortality and have worse disease-free survival compared to those without diabetes.[5] But other authors found that the presence of DM in patients with CRC was not associated with worse cancer-specific survival.[4]

Diabetes mellitus and DM related comorbidities may initiate difficulties during cancer specific

treatment and may have an impact on cancer management and outcome. Colorectal cancer surgery is often followed by postoperative complications which may impact survival. The aim of our study was to find out if DM in patients with advanced colorectal carcinoma is associated with cancer-specific or overall survival.

Patients and methods

This study included 200 consecutive patients (131 males, 69 females, mean age 63 years) with elective colorectal cancer surgery at the Institute of Oncology Ljubljana from September 2010 to March 2013. In 14 patients, curative resection of liver metastases was carried out during the same anesthesia. In all the patients, a laparotomy was performed. The exclusion criteria were preoperative infection, preoperative ileus and palliative surgical procedure.[6,7] All 200 patients were prospectively included in the study about the usefulness of biomarker index CD64 for neutrophils (iCD64n) for early detection of postoperative infection.[6,7] The study protocol was approved by the Republic of Slovenia National Medical Ethics Committee. Approval and written consent for the retrospective study of the long-term outcome of the patients was obtained from the Protocol Review Board (MZ 0120-28/2016-2, ERID-KSOPKR/20), and the Ethics Committee of the Institute of Oncology (ERID-KSOPKR/77, OIRIKE 0049).

Rectum, colon and both of them were affected by cancer in 68%, 30% and 2% of cases, respectively. Stage of tumor was evaluated clinically according to the nuclear magnetic resonance (NMR) investigation before the beginning of the treatment. The TNM classification was used for staging of colorectal cancer disease.[8] Even 64% of patients had Stage 3 or 4 disease, so neo-adjuvant chemotherapy (CTX) and/or radiotherapy (RT) were carried out in 59% of cases. CTX and/or RT were carried out and finished six to eight weeks before surgery, as reported by Golo et al.[9] Each patient was assessed preoperatively according to the American Society of Anesthesiologists (ASA) physical status classification, which accurately predicts morbidity and mortality.[10] Bioelectric impedance analysis (BIA) measurement was performed on the day before the surgery using a portable bioelectrical impedance analyzer BodyStat QuadScan 4000 (Douglas, Great Britain), as already described by Kerin-Povsic et al.[7] Phase angle is the ratio between the reactance and resistance.[11] The illness marker is the ratio between

the impedance measurement at 200kHz and 5kHz. A ratio closer to 1.00 indicates poor cellular health or extreme fluid overload.

DM was found in 39 (19.5%) of patients: 19 were treated only with metformin, 5 only with insulin, while 15 were treated with two or three different oral antidiabetics.

Data about gender, age, body mass index, presence of DM, American Society of Anesthesiologists (ASA) physical status score, stage of disease and postoperative complications were collected prospectively.

All patients had a follow-up at the Institute of Oncology Ljubljana. Cancer-specific survival was defined as the period from the first day of primary treatment (surgery, CTX or RT) to death from colorectal cancer, or the last follow-up. Overall survival was defined as the period from the first day of primary treatment (surgery, CTX or RT) to death from any cause, or the last follow-up. Disease-free survival was defined as the period from the first day of primary treatment to the radiologic or morphologic diagnosis of recurrence, or the last follow-up. The median duration of follow-up was 5.1 years (range 0.2–10.5 years).

The association between categorical variables was tested by the Pearson chi-square test or Fisher's exact test, as appropriate. Univariate analysis was used to identify factors associated with cancer-specific and overall survival. Cancer-specific survival and overall survival were compared by log-rank test. All comparisons were two-sided, and a p-value of <0.05 was considered statistically significant. Survival curves were calculated according to the Kaplan–Meier method. Statistical analyses were performed using the SPSS software (IBM Corp., version 22.0 Armonk, NY).

Results

Data about patient's characteristics, tumor, treatment and outcome are presented in Table 1. The mean age of patients with and without DM was 65 and 62 years, respectively. There was no statistically significant difference in the age of patients with and without DM (p = 0.13). However, patients with DM had a higher ASA score (p = 0.0001) and BMI (p = 0.003) than those without DM. Furthermore, before surgical procedure, the illness marker was higher in patients with DM in comparison to those without DM (p = 0.02). However, higher disease stages were not more common in patients with DM in comparison to those without DM. Stage 3 or 4

TABLE 1. Patient's characteristics, tumor, treatment and outcome

Characteristic		Without diabetes mellitus (N = 161)	With diabetes mellitus (N = 39)	p-value
Age (years) - mean		62.18 (SD ± 11.8)	65.26 (SD ± 8.9)	0.13
Gender	Male	106	25	0.84
	Female	55	14	
American Society of Anesthesiologists physical status classification score	I	14	0	0.0001
	II	95	10	
	III	47	29	
	IV	5	0	
Body mass index (kg/m²) - mean		26.83 (SD ± 4.20)	29.06 (SD ± 4.1)	0.003
Treatment of diabetes	Insulin only	-	5	-
	Metformin only	-	19	
	2 or 3 oral antidiabetics	-	15	
Phase angle (°) - mean		5.47 (SD ±1.0)	5.16 (SD ±0.9)	0.11
Illness marker - mean		0.807 (SD ± 0.036)	0.825 (SD ± 0.049)	0.02
Dry lean body mass (kg) - mean		12.97 (SD ± 4.5)	12.65 (SD ± 4.6)	0.72
Tumor site	Rectum	113	24	0.09
	Colon	47	13	
	Rectum + Colon	1	2	
Stage TNM	0	3	0	0.50
	I	21	6	
	II	33	9	
	III	91	18	
	IV	13	6	
Preoperative radiotherapy	No	67	18	0.61
	Yes	94	21	
Preoperative chemotherapy	No	90	22	0.95
	Yes	71	17	
Surgical procedure	Low anterior resection	73	13	0.38
	Miles + Hartman	38	12	
	Colon resection	50	14	
Synchronous resection of liver metastases	No	151	35	0.48
	Yes	10	4	
Duration of surgery (min) - mean		175 (SD ±66)	199 (SD ±64)	0.034
Loss of blood (mL) -mean		584 (SD ±497)	813 (SD ±812)	0.027
Postoperative transfusion of packed red blood cells (mL) -mean		351 (SD ±516)	603 (SD ±665)	0.011
Postoperative infection (any site)	No	110	22	0.16
	Yes	51	17	
Re-operation	No	153	35	0.21
	Yes	8	4	
Hospital stay (days) -mean		14.4 (SD ±7.6)	19.9 (SD ±10.6)	0.028
Recurrence (N = 181)	No	111	28	0.63
	Locoregional	4	1	
	Distant	26	3	
	Locoregional + distant	7	1	
Outcome	Alive	117	30	0.74
	Dead of disease	34	7	
	Dead of other causes	9	1	
	Dead - Unknown cause	1	1	

disease was found in patients with DM and without DM in 62% and 65%, respectively (p = 0.72). So, also the proportion of patients treated with CTX and/or RT were not statistically different among patients with DM and without DM.

None of the patients had a laparoscopic procedure. A higher proportion of the patients with DM had massive bleeding (p = 0.027) and received blood transfusion (p = 0.011) in comparison to patients without DM. Surgical procedure (p = 0.034) as well as hospital stay (p = 0.028) was longer in patients with DM in comparison to those without DM. None of patients died during the first month after a surgical procedure (p < 0.0001).
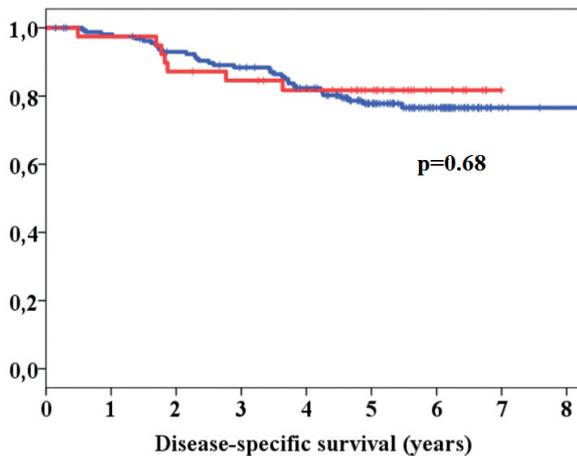
FIGURE 1. Cancer-specific survival of patients with and without Diabetes mellitus (DM).
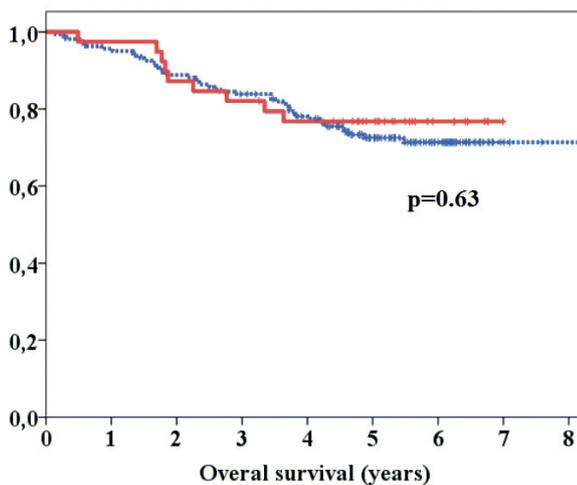
red line = with DM; blue line = without DM

FIGURE 2. Overall survival of patients with and without Diabetes mellitus (DM).

red line = with DM; blue line = without DM

The mean follow-up period was 4.75 years. Recurrence was diagnosed in 23% of patients with DM and in 25% of patients without DM (p = 0.63). Locoregional recurrence was detected in 2/39 (5%) patients with DM and in 11/161 (6.8%) patients without DM. Distant metastases after surgical procedure were detected in 4 patients with DM and 33 patients without DM. Altogether, 41 patients died of cancer and 12 patients of other causes. Cause of death was not statistically different in patients with DM in comparison to those without DM (p = 0.74). Colorectal cancer was the cause of death in 18% and 21% of patients with and without DM, respectively. All causes mortality in patients with DM and without DM was 23% and 27%, respectively.

Three-year cancer-specific survival (Figure 1) in patients with DM and without DM was 85% and 89%, respectively (p = 0.68). Three-year overall survival (Figure 2) in patients with DM and without DM was 82% and 84%, respectively (p = 0.63). Patients with colon and rectal cancer had estimated median survival of 75 and 108 months (p = 0.089), respectively. All patients were included in our statistical analysis of survival because there was only small number of patients with low stage tumor, colon cancer and/or presence of DM which precluded adequate subgroup analysis.

Discussion

The aim of our study was to find out if DM in patients with advanced CRC was associated with cancer-specific and overall survival. In our 200 consecutive patients with elective surgical procedure for CRC, the presence of DM was not associated with cancer-specific or overall survival after the mean follow-up period of 4.75 years. Inversely, a meta-analysis of 26 observational studies on CRC has shown that patients with CRC and DM had a 17% increased risk of overall mortality and a 12% increased risk of cancer-specific mortality compared to those without DM.[5] However, another meta-analysis has shown that persons with CRC and DM had a 32% increase in overall mortality compared to those without DM, but there were no associations between DM and risk of cancer-specific mortality.[4] Bella *et al.* found that the presence of DM was significantly associated with decreased overall and cancer-specific survival.[12] They analyzed 1,039 CRC cases who were included in a EUROCARE-5 high resolution study and were treated in Italy from 2003–2005.[12] Their patients with and without DM did not differ in terms of type of resection, elective versus emergency surgery, or number of lymph nodes examined. Their patients with DM were older in comparison to the patients without DM. Furthermore, diabetics were significantly less likely to receive adjuvant therapy than non-diabetics.[12] But our diabetics were not older than the non-diabetics (p = 0.13) and their overall and cancer-specific survival was not statistically different. A possible explanation is that the same proportion of patients from both groups had preoperative radiotherapy and/or chemotherapy, which might have influenced the survival of patients. Similarly to Bella *et al.*[12], Van de Pol-Franse *et al.*[13] also reported that patients with diabetes and CRC were treated less aggressively compared to those with-

out diabetes. Another possible explanation for the differences in survival among the reported studies is a selection bias between population based and single institution based cohorts of patients. Our patients were treated at a single cancer comprehensive center, while Bella *et al.* report data from seven Italian cancer registries, and Van de Pol-Franse *et al.* report data from the registration area of the Eindhoven Cancer Registry.[12,13] Both of them also included patients treated in general hospitals.

A substantial proportion of deaths in older persons with colorectal cancer can be attributed to chronic heart failure, diabetes mellitus, and chronic obstructive pulmonary disease.[14] Polednak *et al.*[15], in a population-based statewide Connecticut cancer registry, found that the presence of DM was associated with a statistically significantly elevated risk of death from any cause. This finding was due to an elevated risk of death from causes other than CRC.[15] Similarly, Ota *et al.*[16] reported, in 1.216 patients with CRC, that overall survival was significantly inferior in the patients with DM than in those without, but there was no difference in cancer-specific survival between the two groups. Nevertheless, cancer-specific survival was worse in diabetics in stage IV cancer, but it remained unclear whether this has been attributed to differences in malignancy or in treatment.[16] On the other hand, Rao Kondapally Seshasai *et al.*[17] found that DM was moderately associated with deaths from CRC cancer from individual-participant data on 123.205 deaths among 820.900 people in 97 prospective studies. DM worsens prognosis because it is frequently associated with comorbidities such as cardiovascular disease because they are associated with increased risk of death.[12,18,19] Certain comorbidities such as heart problems, alcohol abuse, liver disease, and deep vein thrombosis had an impact on prognosis.[20] Furthermore, the number of comorbid conditions was significant in predicting early mortality.[20] Multimorbidity is common, and exerts a substantial effect on CRC survival.[14] Therefore, comorbidity increases the complexity of cancer management and affects survival duration.[20]

Davila *et al.*[21] studied 30-day mortality using National Veterans Administration administrative data, and found that patients who had received surgical resection more recently had a lower risk of 30-day mortality, compared with those resected in 1987–1988. Significant declines were observed in several postoperative disorders, including anesthesia complications and thromboembolism.[21] Preoperative disorders associated with increased mortality included chronic pulmonary disease, congestive heart failure, diabetes, hemiplegia/paraplegia, moderate/severe liver disease, and renal disease.[21] Obviously, declining preoperative and postoperative disorders, as well as improvements in surgical care, could explain these findings.[21] It is encouraging that none of our patients died during the first month after a surgical procedure. We believe that this reflects the high-quality postoperative care in our ICU and surgical wards. Similar observations were published by Jullumstro *et al.*[22], who studied 1,194 patients treated for CRC at Levanger Hospital during a 25 year period. They found that the presence of DM was not associated with short-term survival or cancer specific survival.[22] An important factor that might have contributed to the smoother postoperative course and low 30-day mortality in our center is our policy that all patients with malnutrition and/or cachexia had nutritional interventions and pharmacological therapy.[23,24] It is well known that a low fat-free mass is associated with 28-day mortality after admission to the ICU.[25] In our patients with DM, the illness marker and BMI were higher in comparison to those without DM. Furthermore, diabetics had a higher ASA score, which reflects a worse general condition and concomitant diseases. Our patients did not differ in tumor stage, but a higher proportion of patients with DM had massive bleeding and received blood transfusion in comparison to patients without DM. Therefore, it was not surprising that surgical procedure as well as hospital stay was longer in patients with DM in comparison to those without DM.

Jeon *et al.*[26] observed that DM was significantly associated with worse overall survival and recurrence-free survival in colon cancer patients, while there was no association with the presence of DM and overall or disease-free survival in rectal cancer patients. This study in 4,131 patients with CRC suggests that DM negatively impacts survival outcomes of patients with colon cancer but not rectal cancer.[26] Similarly, in colon cancer patients, Meyerhardt *et al.*[27], in a large randomized adjuvant chemotherapy trial of 3,759 patients treated between 1988 and 1992, found that patients with DM experienced a significantly higher rate of overall mortality and cancer recurrence, and an increase in treatment-related diarrhea. Also Huang *at al.*[28] reported that DM was a poor prognostic factor for overall and cancer-specific survival in 2,762 consecutive patients diagnosed with colon cancer in Taipei Veterans General Hospital. However, Shonka *et al.*[29] found no significant relationship be-

tween stage of colon cancer or survival and presence of DM in 1,853 patients with colon cancer treated in a single institution during an 18-year period. On the other hand, Bella *et al.*[12] found that the presence of DM had a stronger adverse effect on rectal than colon cancer prognosis in 1,039 patients with CRC. Cancer-specific mortality was significantly higher among diabetics, while colon cancer-specific mortality was only non-significantly higher, even though overall mortality was significantly higher.[12] In our patients with colon and rectum cancer, overall and cancer-specific survival was not statistically different, but the number of patients was too small to allow any reliable conclusions about possible differences in prognosis.

A limitation of this study is that it is retrospective, and the follow-up period is relatively short. Furthermore, there were only a small number of diabetics, which precluded analysis of the association between diabetes, stage of disease, location of cancer (rectum versus colon) and survival. Other limitations are the lack of information about diabetes type and age of diabetes onset, as well as the type and duration of diabetic therapy. Because of the relatively small number of diabetics, we could not analyze the association between different diabetic therapies (metformin and insulin) on outcome of patients. On the other hand, an advantage of our study is that a large proportion of patients had an advanced stage of disease with a higher risk of recurrence or progression of disease. All our patients were followed at our institution, so our data on recurrence and cause of death are very reliable.

Conclusions

The presence of DM was not associated with tumor stage, disease-specific survival or overall survival in a group of patients with advanced colorectal carcinoma treated at a cancer comprehensive center.

Acknowledgements

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