RESEARCH ARTICLE

Editorial Process: Submission:05/17/2023 Acceptance:01/22/2024

Type 2 Diabetes Mellitus and Non-Metastatic Colorectal Cancer: A Retrospective Study on Survival and Toxicity Profiles

Naglaa Said Elabd[1], Mahmoud Magdy Alabassy[2], Randa Mohamed Seddik[1]*, Amany A. Amer[1], Reham Ahmed Abdelaziz[3], Ahmed Sohaib[3]

Abstract

Background and aims: Being one of the most common cancers accounting for approximately 185 million cases globally, colorectal cancer (CRC) is one of the leading derivers of cancer-related mortalities. A high prevalence of Type 2 diabetes mellitus and CRC was noted, together with a causal link between diabetes and CRC development. Thereby, the goal of this study was to properly evaluate type 2 Diabetes mellitus in non-metastatic colorectal cancer patients, and to highlight its impacts on patient's outcome. **Methods:** Patients with non-metastatic colorectal cancer diagnosed between January 2016 and December 2020 were studied retrospectively. Patients were divided into two groups based on whether or not they had type II diabetes. The clinico-pathological, laboratory, treatment and survival data were gathered. **Results:** A total of 318 patients were included in this study. The toxicity of the drugs used in CRC patients receiving the treatment protocols (169 in non-T2DM group and 39 in T2DM group), both groups reported close percentage of side effects and a similar frequency of drug toxicity occurrence as well as grade of toxicity, with the exception of neuropathy, which was more common in the T2DM group (33.3% vs 11.2%). As for prognosis, non-T2DM and T2DM patients had a mean progression free survival of (71.4 and 60.83 months, respectively) ($p = 0.019$). Overall survival was 73.1% for T2DM and 85.3% for non T2DM cases. The median overall survival was not reached for both groups in terms of overall survival. **Conclusion:** T2DM is considered a risk factor for poor survival among CRC patients. Treatment related toxicity is not affected by the presence or absence of diabetes, yet neuropathy needs further studies for diabetic patients receiving oxaliplatin.

Keywords: Colorectal cancer- type 2 diabetes mellitus- survival- toxicity

Asian Pac J Cancer Prev, **25 (1)**, 87-94

Introduction

Being one of the most common cancers accounting for approximately 185 million cases globally, colorectal cancer (CRC) is one of the leading derivers of cancer-related mortalities, contributing to nearly 700,000 deaths annually [1]. Despite the availability of treatment strategies for CRC, radical resection remained the gold standard [2].

Numerous variables have been associated to the development of CRC, which may be divided into lifestyle or behavioral variables and underlying genetic variables. A higher likelihood of CRC was found in individuals with a family history of cancer, colon polyps, inflammatory bowel disease (IBD), or diabetes mellitus. What's more, the gut microbiome, race, socioeconomic status, gender, age, have all been linked to an increased risk of CRC. Physical inactivity, obesity, consumption of alcohol, smoking, and inappropriate dietary patterns such as diet rich in red meat and low in fiber have all been accused of being involved as significant risk factors for CRC [3].

Type 2 diabetes mellitus (T2DM) is a metabolic disease that imposes a substantial burden on both individuals and society worldwide and is associated with higher mortality and morbidity [4]. Further to that, T2DM may increase the likelihood of digestive cancers such as colorectal cancer [5], gastric cancer [6], and esophageal cancer [7]. Besides the impact on the onset of the tumor, T2DM might influence the patient's outcome including disease-free survival and overall survival [5]. The lineament of T2DM is its association with insulin resistance and even in the vast majority of cases, compensatory hyperinsulinemia [8].

Cancer and type 2 diabetes are two worldwide public health issues that are additionally considered the world's most lethal and disabling illnesses. They share several risk factors (high blood pressure, obesity, hyperlipidemia) and

*[1]Tropical Medicine department, Faculty of Medicine, Menoufia University, Shebin Elkom, Menoufia, Egypt. [2]General surgery department, Faculty of Medicine, Menoufia University, Shebin Elkom, Menoufia, Egypt. [3]Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Menoufia University, Shebin Elkom, Menoufia, Egypt. *For Correspondence: randa.sedeek@med.menofia.edu.eg*

an etiological mechanism. Both share several risk factors (hyperlipidemia, obesity, and high blood pressure) and an etiological mechanism [9].

Some proposed mechanisms among both T2DM and CRC may make a significant contribution to tumor evolution, such as hyperglycemia, that further promotes tumor cell proliferation. Moreover, T2DM, along with obesity, is indeed a chronic low-grade inflammatory disease that can lead to malignant tumors. Over and above, hyperinsulinemia may promote tumor cell mitosis and metastasis [10].

In light of the high prevalence of T2DM and CRC, along with reviews of published research demonstrating a causative link for T2DM in CRC development [11]. More researches are needed to determine the likelihood of relationship between these two illnesses. Thereby, the goal of this study was to properly evaluate type 2 Diabetes mellitus in Egyptian patients with non-metastatic colorectal cancer, and to highlight its impacts on patient's outcome.

Materials and Methods

This retrospective study was carried out in Clinical Oncology and Nuclear medicine department in collaboration with Tropical Medicine department, Faculty of Medicine, Menoufia University. It was performed on patients with non-metastatic colorectal cancer diagnosed and treated at department of Clinical Oncology and Nuclear medicine, during the period between January 2016 and December 2020. Patient's clinical data were collected from the files archived at the department. The inclusion criteria were pathologically proven colorectal cancer (TNM stage I-III), not having any other known malignancy. Distant metastasis at time of diagnosis and files with non-conclusive data about the history of diabetes were the exclusion criteria.

The studied patients were classified into two groups according to the presence of type II diabetes mellitus at time of cancer diagnosis. Demographic data, anthropometric measurement, clinical data, laboratory investigational data and treatment data were collected from all patients 'files. Demographic data included sex, age, smoking history, family history of colorectal cancer and history of associated comorbidities.

Anthropometric measurement included weight, height, body mass index (BMI) and clinico-pathological data included patient performance status (PS), site of the tumor, presenting symptom(s), grade, TNM stage, total number of removed lymph nodes and number of involved lymph nodes by the tumor were reported. Laboratory investigational data at time of the patient diagnosis included complete blood count [white blood cells SWBCs), hemoglobin concentration (Hb), and platelet counts], AST, ALT, tumor markers [Carcinoembryonic antigen (CEA) and Carbohydrate antigen 19-9 (CA19.9)].

Treatment data included type of surgery done, types of adjuvant treatment protocols, treatment related toxicity and duration of the therapy. Toxicities were assessed regarding to Common Terminology Criteria for Adverse Events (CTCAE) [12]. Survival data included progression free survival and overall survival

Survival data

Progression free survival (PFS) was calculated from the date of diagnosis to the date of disease progression for patients with relapsed disease or date of last follow up for patients in complete response (radiological progression or pathological progression). Overall survival (OS) was calculated from the date of diagnosis to the date of death or the date of last documented follow up for patients contacted by phone.

Ethical Approval

The research was conducted out with the approval of the ethical committee, Faculty of Medicine, Menoufia University (IRP number: 11/2022TROP19-2), and in accordance with the Helsinki Declaration.

Statistical analysis of the data

The data were supplied to the computer and were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Numbers and percentages were used to represent categorical data. The Chi-square test was employed to compare between two groups. Alternatively, Fisher Exact or Monte Carlo correction test was applied when more than 20% of the cells have expected count less than 5. For continuous data, they were tested for normality by the Kolmogorov- Smirnov. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median for normally distributed quantitative variables Student t-test was used to compare two groups. On the other hand, for not normally distributed quantitative variables Mann Whitney test was used to compare two groups. For the significant relationship between the presence of T2DM and the overall survival and progression free survival, the Kaplan-Meier survival curve and Cox regression were applied. Significance of the obtained results was judged at the 5% level

Results

A total of 318 patients were included in this study and they were selected from 612 patients with colorectal cancer who recorded during the study period. 264 patients were excluded as 234 patients of them had metastatic colorectal cancer and 30 patients were with non-conclusive data and their files weren't completed. There were 52 patients with T2DM and 266 patients without T2DM. The mean age in the diabetic group was considerably lower (48.8 ±12.1 years) compared to that of the non-diabetic group (52.7±11.6 years) with p=0.031. Additionally, we noticed that T2DM group had a significantly higher BMI (p=0.018) and a higher rate of smoking (p=0.002). However, a non-significant difference was found in terms of gender, family history of CRC, and comorbid diseases (p = 0.369, 0.634, and 1.000 respectively) (Table 1).

Clinically, abdominal pain and bleeding per rectum were the most frequent presenting symptoms in both groups, nevertheless, dysuria and vomiting were the least ones with a statistical insignificant difference between the two groups. Likewise, the performance status (PS) score

Table 1. Comparison between the Two Studied Groups According to Demographic Data, Anthropometric Measurement and Clinical Data

	Non-T2DM (n = 266)	T2DM (n = 52)	p
Sex			
Male	151 (56.8%)	26 (50%)	0.369
Female	115 (43.2%)	26 (50%)	
Age (/years)			
Mean ± SD.	52.7 ± 11.6	48.8 ± 12.1	0.031*
Median (Min. – Max.)	54 (22 – 73)	48.5 (26 – 71)	
Weight (kg)			
Mean ± SD.	81.9 ± 11.4	83.7 ± 7.3	0.141
Median (Min. – Max.)	82 (60 – 110)	83 (70 – 103)	
Height (cm)			
Mean ± SD.	168.5 ± 7	166.6 ± 7	0.065
Median (Min. – Max.)	169 (153 – 183)	168 (154 – 178)	
BMI (kg/m^2)			
Mean ± SD.	29 ± 4.6	30.3 ± 3.5	0.018*
Median (Min. – Max.)	28.2 (20.3 – 41.5)	29.6 (24.4 – 40)	0.002*
History of smoking	33 (12.4%)	15 (28.8%)	
Family history of CRC	25 (9.4%)	6 (11.5%)	0.634
Comorbid diseases	23 (8.6%)	4 (7.7%)	^{FE}p=1.000
Clinical presentation			
Bleeding	57 (21.4%)	13 (25%)	^{MC}p= 0.452
Anemia	34 (12.8%)	4 (7.7%)	
Constipation	26 (9.8%)	5 (9.6%)	
Abdominal pain	63 (23.7%)	13 (25%)	
Melena	17 (6.4%)	2 (3.8%)	
Obstruction	37 (13.9%)	10 (19.2%)	
Piles	13 (4.9%)	2 (3.8%)	
Weight loss	17 (6.4%)	1 (1.9%)	
Dysuria	2 (0.8%)	1 (1.9%)	
Vomiting	0 (0%)	1 (1.9%)	
PS			
0	245 (92.1%)	49 (94.2%)	^{MC}p= 0.188
1	17 (6.4%)	1 (1.9%)	
2	4 (1.5%)	2 (3.8%)	
Site of CRC lesion			
Rectum	67 (25.2%)	15 (28.8%)	0.857
Ascending colon	85 (32%)	16 (30.8%)	
Descending colon	114 (42.9%)	21 (40.4%)	
Concomitant benign polyps	35 (13.2%)	6 (11.5%)	0.75
Grade			
I	25 (9.4%)	7 (13.5%)	0.421
II	153 (57.5%)	32 (61.5%)	
III	88 (33.1%)	13 (25%)	
Stage			
I	11 (4.1%)	2 (3.8%)	0.029*
II	144 (54.1%)	18 (34.6%)	
III	111 (41.7%)	32 (61.5%)	
LN metastasis			
Mean ± SD.	2.8 ± 4.1	4.6 ± 5	0.004*
Median (Min. – Max.)	0 (0 – 20)	3.5 (0 – 18)	

CRC, colorectal cancer; LN, lymph node; SD, Standard deviation; FE, Fisher Exact; MC, Monte Carlo; p, p value for comparing between the two studied groups; *, Statistically significant at p < 0.05

Table 2. Comparison between the Two Studied Groups According to Laboratory Investigation and Treatment

	Non-T2DM (n = 266)	T2DM (n = 52)	p
Hb% (gm/dl)			
Mean ± SD.	10.6 ± 1.6	11 ± 1.4	0.08
Median (Min. – Max.)	10.9 (6 – 13.6)	11.2 (7.5 – 13.9)	
WBCs (×10^3/mm^3)			
Mean ± SD.	7.3 ± 2.2	7.5 ± 2.2	0.419
Median (Min. – Max.)	6.9 (3.9 – 12)	7.3 (4 – 12)	
Platelets (×10^3/mm^3)			
Mean ± SD.	372.6 ± 108.4	366.4 ± 114	0.708
Median (Min. – Max.)	351 (103 – 568)	335.5 (163 – 573)	
ALT (IU/L)			
Mean ± SD.	36.2 ± 10.5	40.6 ± 11.3	0.006*
Median (Min. – Max.)	37 (14 – 58)	42 (21 – 80)	
AST (IU/L)			
Mean ± SD.	35.2 ± 10.5	35.4 ± 10.8	0.908
Median (Min. – Max.)	36 (13 – 56)	39 (16 – 54)	
CEA (mg/dl)			
Mean ± SD.	13.3 ± 15.4	18.5 ± 18.5	0.005*
Median (Min. – Max.)	5 (1 – 90)	9.5 (1 – 82)	
CA19-9 (U/ml)			
Mean ± SD.	197.3 ± 120.4	237.1 ± 130.7	0.047*
Median (Min. – Max.)	190 (12 – 540)	228 (23 – 430)	
Type of surgery			
Low anterior resection	56 (21.1%)	9 (17.3%)	0.184
Abdominoperineal resection	11 (4.1%)	6 (11.5%)	
Right hemicolectomy	85 (32%)	16 (30.8%)	
Left hemicolectomy	114 (42.9%)	21 (40.4%)	
Number of removed LN			
Mean ± SD.	21.4 ± 6.6	21.1 ± 7	0.62
Median (Min. – Max.)	20 (2 – 45)	19 (9 – 37)	
Treatment protocol			
Only CCRT	27 (10.2%)	2 (3.8%)	0.219
XELOX	45 (16.9%)	14 (26.9%)	
XELODA	22 (8.3%)	4 (7.7%)	
FOLFOX	38 (14.3%)	8 (15.4%)	
CCRT+ XELOX	12 (4.5%)	5 (9.6%)	
CCRT+ FOLFOX	25 (9.4%)	6 (11.5%)	
Follow up	97 (36.5%)	13 (25%)	
Duration of treatment			
Mean ± SD.	3.2 ± 2.9	4.2 ± 2.8	0.049*
Median (Min. – Max.)	3 (0 – 8)	6 (0 – 8)	
Receiving medications	21 (7.9%)	52 (100%)	<0.001*
Mortality	39 (14.7%)	14 (26.9%)	0.030*
Relapse	56 (21.1%)	19 (36.5%)	0.016*

SD, Standard deviation; p, p value for comparing between the two studied groups; *, Statistically significant at p ≤ 0.05

didn't differ significantly between T2DM and non-T2DM groups with good performance (PS0) being the most frequent. The descending colon was the commonest site of CRC lesion followed by ascending colon and rectum in both groups, and concomitant benign polyps were present in 11.5% and 13.2% of T2DM and non-T2DM groups respectively. In terms of tumor stage, 61.5% of

Table 3. Comparison between the Two Studied Groups According to Drug Toxicity#

	Non-T2DM (n = 169)		T2DM (n = 39)		p
	Toxicity No. (%)	Grade of toxicity Median (Min. – Max.)	Toxicity No. (%)	Grade of toxicity Median (Min. – Max.)	
None	1 (0.6%)	0 (0 – 0)	1 (2.6%)	0 (0 – 0)	FEp=0.341
Vomiting	20 (11.8%)	2 (1 – 3)	2 (5.1%)	3 (2 – 3)	FEp=0.384
Diarrhea	62 (36.7%)	2 (1 – 3)	10 (25.6%)	2 (2 – 3)	0.191
Hand-foot syndrome	28 (16.6%)	2 (1 – 3)	7 (17.9%)	2 (2 – 3)	0.835
Mucositis	15 (8.9%)	2 (1 – 3)	1 (2.6%)	2 (2 – 2)	FEp=0.316
Neuropathy	19 (11.2%)	2 (1 – 2)	13 (33.3%)	2 (1 – 3)	0.001*
Neutropenia	22 (13%)	2 (1 – 3)	4 (10.3%)	3 (2 – 4)	FEp=0.792
Skin maceration	2 (1.2%)	3 (3 – 3)	1 (2.6%)	3 (3 – 3)	FEp=0.465

#, Excluded patients whom treatment protocol was follow up; FE: Fisher Exact; p: p value for comparing between the two studied groups; *, Statistically significant at $p \leq 0.05$

Table 4. Kaplan-Meier Survival Curve for Overall Survival and Progression Free Survival (in Months)

	Mean	Median	% End of study	Log rank χ^2 (p)	HR (LL – UL 95%C.I)	p-value
Overall survival						
Non-T2DM	75.44	–	72.2	5.034*	1	0.028*
T2DM	66.14	–	51.6	(0.025*)	1.985 (1.076 – 3.662)	
Progression free survival						
Non-T2DM	71.4	–	67.5	5.707*	1	0.019*
T2DM	60.83	69	46	(0.017*)	1.864 (1.107 – 3.140)	

HR, Hazard ratio; C.I, Confidence interval; LL, Lower limit; UL: Upper Limit; *, Statistically significant at $p < 0.05$

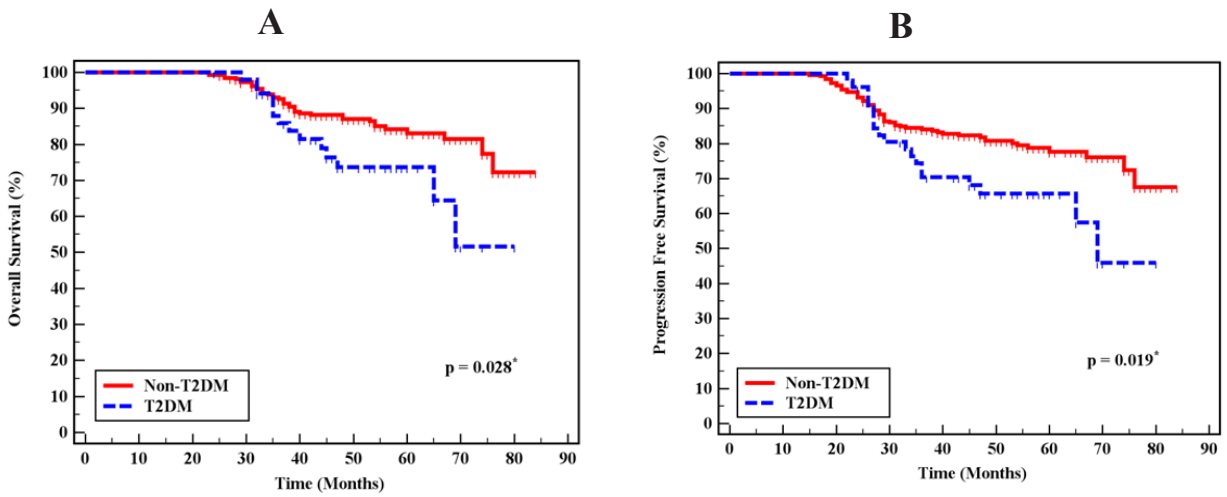

Figure 1. A&B, Mean progression free survival between studied groups.

T2DM patients had stage III tumors compared to 41.7% of non-T2DM patients, with a statistically significant difference (p = 0.029). Analogously, the number of involved lymph nodes by the tumor was significantly greater in the T2DM group than in the non-T2DM group (p = 0.004). The tumor grade, notwithstanding, did not differ significantly between the two groups (p = 0.421) as displayed in Table 1.

Regarding the laboratory investigations of the studied groups, we noticed that the T2DM group has significantly higher ALT, CEA, and CA19-9 levels than the non-T2DM group (p = 0.006, 0.005, and 0.047, respectively). Concerning the surgical management, neither group differed in terms of the type of surgery performed or the number of LN removed. Furthermore, neither group varied in terms of post-surgical treatment protocols where no treatment was required (just follow up), and chemotherapy with XELOX protocol were the most commonly used regimens in both groups. The duration of treatment, however, was significantly longer in the T2DM group (p=0.049). What's more, the T2DM showed higher mortality and relapse rates than the non-T2DM group (p =

Table 5. Univariate and Multivariate COX Regression Analysis for the Parameters Affecting Overall Survival (n = 318)

	Univariate		#Multivariate	
	p	HR (LL – UL 95%C.I)	p	HR (LL – UL 95%C.I)
DM	0.028*	1.985 (1.076 – 3.662)	0.78	0.912 (0.478 – 1.740)
Presence of LN metastasis	<0.001*	114.5 (11.267 – 1163.0)	0.856	66230.5 (0.0 – 6.1×10^{56})
CEA (mg/dl)	<0.001*	1.068 (1.056 – 1.080)	<0.001*	1.039 (1.023 – 1.055)
CA19-9 (U/ml)	<0.001*	1.010 (1.007 – 1.012)	0.001*	1.004 (1.002 – 1.007)
BMI (kg/m^2)	0.247	1.035 (0.977 – 1.096)		
Presence of history of smoking	0.589	1.220 (0.593 – 2.511)		
Age (/years)	0.836	0.998 (0.975 – 1.021)		
Presence of Family history of CRC	0.731	1.161 (0.496 – 2.716)		
Site of CRC lesion Presence of				
Rectum	0.959	0.984 (0.534 – 1.813)		
Ascending colon	0.183	1.479 (0.832 – 2.630)		
Descending colon	0.262	0.728 (0.419 – 1.267)		
Clinical presentation Presence of				
Obstruction	0.994	0.997 (0.470 – 2.116)		
Weight loss	0.963	1.028 (0.320 – 3.299)		
Anemia	0.684	0.826 (0.328 – 2.075)		

HR, Hazard ratio; C.I, Confidence interval; LL, Lower limit; UL, Upper Limit; #, All variables with p<0.05 was included in the multivariate; *, Statistically significant at p ≤ 0.05

Table 6. Univariate and ىultivariate COX Regression Analysis for the Parameters Affecting Progression Free Survival (n = 318)

	Univariate		#Multivariate	
	p	HR (LL – UL 95%C.I)	p	HR (LL – UL 95%C.I)
DM	0.019*	1.864 (1.107 – 3.140)	0.914	0.971 (0.569 – 1.656)
Presence of LN metastasis	<0.001*	119.4 (16.776 – 849.19)	0.845	149821.9 (0.0 – 1.63×1057)
CEA (mg/dl)	<0.001*	1.061 (1.051 – 1.072)	<0.001*	1.026 (1.012 – 1.040)
CA19-9 (U/ml)	<0.001*	1.009 (1.007 – 1.011)	<0.001*	1.004 (1.002 – 1.006)
BMI (kg/m2)	0.085	1.044 (.994 – 1.096)		
Presence of history of smoking	0.691	1.134 (0.610 – 2.108)		
Age (/years)	0.785	0.997 (0.978 – 1.017)		
Presence of Family history of CRC	0.756	1.123 (0.540 – 2.339)		
Site of CRC lesion Presence of				
Rectum	0.657	0.887 (0.522 – 1.507)		
Ascending colon	0.111	1.474 (0.915 – 2.374)		
Descending colon	0.298	0.782 (0.491 – 1.243)		
Clinical presentation Presence of				
Obstruction	0.462	0.770 (0.384 – 1.546)		
Weight loss	0.641	1.241 (0.501 – 3.077)		
Anemia	0.221	1.471 (0.793 – 2.729)		

HR, Hazard ratio; C.I, Confidence interval; LL, Lower limit; UL, Upper Limit; #, All variables with p<0.05 was included in the multivariate; *, Statistically significant at p ≤ 0.05

0.03 and 0.016 respectively) as shown in Table 2.

Table 3 demonstrated the toxicity of the drugs used in CRC patients receiving the treatment protocols (169 in non-T2DM group and 39 in T2DM group). Analysis of our data displayed that both non-T2DM and T2DM patient groups reported close percentage of side effects of the treatment protocol used. Our data analysis showed that both non-T2DM and T2DM patients reported a similar frequency of occurrence of drug toxicity as well as the grade of toxicity, with the exception of neuropathy, which was more common in the T2DM group than the non-T2DM group (33.3% vs 11.2%) with a more advanced toxicity grade. Additionally, we noticed that diarrhea is a frequent side effect in both groups.

To analyze the effect of T2DM on overall survival and progression free survival in non-metastatic CRC,

Kaplan–Meier survival curve and a log-rank (Mantel-Cox) analysis were applied. Non-T2DM patients had a mean overall survival of 75.44 months, while T2DM patients had a mean overall survival of 66.14 months (p = 0.028). In parallel to these results, non-T2DM and T2DM patients had a mean progression free survival of (71.4 and 60.83 months, respectively) (p = 0.019) as illustrated in Table 4 and Figures 1A, B. Importantly, we observed that the presence of T2DM was a significant risk for poor overall survival and progression free survival in non-metastatic CRC (p = 0.028 and 0.019 respectively), HR (LL – UL 95%CI) was 1.985 (1.076 – 3.662) and 1.864 (1.107 – 3.140) respectively (table 4).

Overall survival was 73.1% for T2DM and 85.3% for non T2DM cases. The median overall survival was not reached for both groups in terms of overall survival. However, median PFS was 69 months for T2DM group and not reached for non T2DM group

For the parameters influencing overall survival in non-metastatic CRC patients, the univariate and multivariate logistic regression analyses revealed the following: with the univariate test T2DM had p = 0.028 HR 1.985 (1.067–3.662), the presence of lymph node metastasis had p < 0.001 HR 114.5 (11.267–1163), CEA had p < 0.001 HR 1.068 (1.056–1.080), and CA19-9 had p <0 .001 HR 1.010 (1.007–1.012), which could be meaningful in overall survival prediction. On the other hand, in the multivariate analysis only CEA p < 0.001, HR1.039 (1.023–1.055) and CA19-9 p=0.001, HR 1.004 CI=1.002–1.007) were independent predictors for overall survival (Table 5). Similarly, T2DM, the presence of lymph node metastasis, CEA, and CA19-9 were all significant predictors of progression free survival in the univariate, but still only CEA and CA19-9 were independent predictors of progression free survival in the multivariate analysis as displayed in table 6.

Discussion

Diabetes mellitus could have a substantial impact on one's quality of life. Diabetes not only provokes neurological and vascular complications, but it is also linked to cancer occurrence, development, and prognosis [8]. CRC is the world's third leading cause of death and fourth most commonly diagnosed cancer [13]. A number of epidemiological studies have found that individuals with T2DM have a higher likelihood of developing CRC compared with their non-diabetic counterparts [14-16]. The coexistence of diabetes pandemics and the growing global cancer burden has sparked interest in determining the epidemiological and biological links among these medical issues. Thus, the purpose of this study was to properly assess type 2 diabetes mellitus in Egyptian patients with non-metastatic CRC and to identify its effects on patient outcome.

The current retrospective study was carried out on patients with non-metastatic colorectal cancer who were diagnosed, treated and followed up at departments of Clinical Oncology and Nuclear medicine, and Tropical Medicine during 5 years between January 2016 and December 2020. During this time period, a total of 318 patients were included, with 52 (16.4%) of them experiencing T2DM. The mean age in the diabetic group was considerably lower compared to that of the non-diabetic group and we noticed that T2DM group had a significantly higher BMI and a higher rate of smoking, however, a non-significant difference was found in terms of gender, family history of CRC, or comorbid diseases. In a study that looked at surgically resected colorectal cancer rates in Korea between 1997 and 2004, 11.0% (58/528) of the patients had T2DM [16]. Additionally, a retrospective study on Chinese population found that of a total 4250 CRC patients 12.25% had T2DM. Consistent with our findings, those with T2DM had higher BMI, didn't differ by gender or family history. However, they were older and had more frequent comorbid diseases [17]. This difference could be attributed to discrepancies in population characteristics.

Many factors influenced the prognosis of CRC, which would include age, stage of tumor, and existence of complications [18]. In the current study we noticed that, 61.5% of T2DM patients had stage III tumors compared to 41.7% of non-T2DM patients, besides, the number of involved lymph nodes by the tumor was significantly greater in the T2DM group than in the non-T2DM group. Cheng et al. 2022 [17] hypothesized that T2DM and its related comorbidities could actually impact prognosis in early tumor stages, whereas the tumor itself might influence prognosis in advanced tumor stages.

The relationship between diabetes and CRC prognosis could be explained primarily by the influence of hyperinsulinemia, insulin resistance (IR), in addition to cancer pathogenesis on the insulin/insulin-like growth factor (IGF) system, which itself is crucial in CRC pathogenesis, progression, as well as prognosis. IGF-1's insulin-like effects when it interacts with associated receptors such as IGF-1R, IR, or hybrid receptors perform a critical role in maintaining normal glucose homeostasis and the pathogenesis of diabetes [19]. It is well known that, insulin resistance (IR) causes a compensatory increase in insulin secretion in diabetic patients, and by inhibiting IGF binding proteins, this hyperinsulinemia could enhance the IGF-1 biological activity, that is antiapoptotic and mitogenic factor [20]. Insulin-like growth factors, over and above, activate the IGF-1R, increasing its expression in cancer cells, and afterwards activating a number of intracellular signaling cascades that inhibit apoptosis and promote cell cycle progression [19]. Ding et al. reported over expression of IGF-1, IGF-1R and IR in CRC patients with T2DM than those without [20].

Concerning the management in both patients' groups, we found that neither group differed in terms of the type of surgery performed, the number of LN removed, or the post-surgical treatment protocols. However, the duration of treatment was significantly longer in the T2DM group and the T2DM patients showed higher mortality and relapse rates. All patients at our institution are treated according to the international standard guidelines. So, the difference in treatment duration between the two groups may be attributed to the higher stage seen with T2DM group. It is known that higher stages in CRC need more duration and combined treatment modalities. Stage I

CRC is treated only surgically while stage II may need post-surgical adjuvant single agent chemotherapy with capecitabine or a short duration (3 months) of multiagent chemotherapy with XELOX regimen. Stage III CRC is usually treated by a longer duration (6 months) of multiagent chemotherapy. Adding to this, if the primary tumor is within the rectum radiotherapy is used as a neoadjuvant treatment which also prolongs the duration of treatment and adds-on to toxicity [21].

It has been recognized that, insulin/IGF-dependent pathways activation is a crucial step making a contribution to several mechanisms of CRC resistance to both conventional and targeted therapeutic agents, resulting in enhanced PI3K/Akt signaling that prohibits chemotherapeutic drug-induced apoptosis and desensitizes CRC cells to the effect of anti-EGFR antibodies that are used in the metastatic setting [22]. Furthermore, Caudle et al. 2008 [23] reported that rectal cancer patients with diabetes had a lower response rate to chemoradiotherapy than those without.

Oxaliplatin is one of the agents used in the treatment regimens of CRC. It is known for its neuro-toxic effect. In our study, we identified a significant difference in neuropathy experienced between both groups being more evident in diabetic patients. This finding suggests that diabetes may enhance the neurotoxicity of oxliplatin. It is worthy saying that the number of patients with neuropathy was not that high to generalize this finding, but it needs further research on a higher number of patients.

This finding is also supported by a study done on 62 patients at Albert-Einstein cancer center. The researchers found out that patients with diabetes developed neuropathy at a lower cumulative dose of oxaliplatin [24]. The Kaplan-Meier survival curve and a log-rank (Mantel-Cox) analysis were used to investigate the impact of T2DM on overall survival and progression free survival in non-metastatic CRC. T2DM was found to be a significant risk factor for poor overall survival and progression-free survival in non-metastatic CRC.

Zhu et al. 2017 [19] conducted a meta-analysis study that looked at both the 5-year survival rate and the survival risk, that further mirrored the impact of diabetes on CRC prognosis. According to the findings, patients with diabetes have a lower 5-year survival rate in colorectal, colon, and rectal cancers, with 18%, 19%, and 16% lower survival rates, respectively. However, Amshoff et al. and Huang et al. found no association between T2DM in CRC patients and disease-specific or all-cause survival [25, 26]. Possible explanations for disparities in observations throughout studies involve T2D duration and severity; negative impacts of T2D on survival might indeed depend on years of T2D experience, as evidenced by differential risk estimates based on the disease duration.

According to Lin et al. 2021 [27] diabetic patients with CRC have a higher mortality rate than non-diabetic patients, and it is critical to control and manage DM-associated disorders in order to improve survival in patients with CRC patients with T2DM. Furthermore, Mills et al. 2013 [28] found that diabetes was linked with a 17% increased risk of all-cause mortality in CRC patients in a meta-analysis of 21 studies. As well, Dehal et al. 2012 [29] attributed the cause of this association to the general consequences that diabetes has on mortality, such as increased death from cardiovascular disease and perioperative mortality.

In conclusion, patients with T2DM develop CRC at a younger age than non-diabetics and they usually present at a higher stage of the disease that may need longer treatment durations. T2DM is considered a risk factor for poor survival among CRC patients. Treatment related toxicity is not affected by the presence of absence of diabetes, yet neuropathy needs further studies for diabetic patients receiving oxaliplatin.

Author Contribution Statement

All authors made significant contributions to the work presented, whether in the areas of ideation, study design, implementation, data collection, analysis, and interpretation, or all of these. They also contributed to the article's writing, revising, or critical evaluation, gave final approval for the version to be published, chose the journal to which the article was submitted, and agreed to be responsible for all aspects of the work.

Acknowledgements

Ethical Approval

The research was conducted out with the approval of the ethical committee, Faculty of Medicine, Menoufia University (IRP number: 11/2022TROP19-2), and in accordance with the Helsinki Declaration.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492.
2. Peng D, Cheng YX, Cheng Y. Improved overall survival of colorectal cancer under multidisciplinary team: A meta-analysis. Biomed Res Int. 2021;2021:5541613. https://doi.org/10.1155/2021/5541613.
3. Sawicki T, Ruszkowska M, Danielewicz A, Niedźwiedzka E, Arłukowicz T, Przybyłowicz KE. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. Cancers (Basel). 2021;13(9). https://doi.org/10.3390/cancers13092025.
4. Roy A, Sahoo J, Kamalanathan S, Naik D, Mohan P, Kalayarasan R. Diabetes and pancreatic cancer: Exploring the two-way traffic. World J Gastroenterol. 2021;27(30):4939-62. https://doi.org/10.3748/wjg.v27.i30.4939.
5. Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic

review. World J Gastroenterol. 2015;21(19):6026-31. https://doi.org/10.3748/wjg.v21.i19.6026.
6. Peng D, Cheng YX, Zhang W. Does roux-en-y construction really bring benefit of type 2 diabetes mellitus remission after gastrectomy in patients with gastric cancer? A systematic review and meta-analysis. Diabetes Ther. 2020;11(12):2863-72. https://doi.org/10.1007/s13300-020-00934-7.
7. Xu B, Zhou X, Li X, Liu C, Yang C. Diabetes mellitus carries a risk of esophageal cancer: A meta-analysis. Medicine (Baltimore). 2017;96(35):e7944. https://doi.org/10.1097/md.0000000000007944.
8. Klil-Drori AJ, Azoulay L, Pollak MN. Cancer, obesity, diabetes, and antidiabetic drugs: Is the fog clearing? Nat Rev Clin Oncol. 2017;14(2):85-99. https://doi.org/10.1038/nrclinonc.2016.120.
9. Abudawood M. Diabetes and cancer: A comprehensive review. J Res Med Sci. 2019;24:94. https://doi.org/10.4103/jrms.JRMS_242_19.
10. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: A consensus report. Diabetes Care. 2010;33(7):1674-85. https://doi.org/10.2337/dc10-0666.
11. Jin T. Why diabetes patients are more prone to the development of colon cancer? Med Hypotheses. 2008;71(2):241-4. https://doi.org/10.1016/j.mehy.2008.03.025.
12. U.S. Department of health and human services (2017). Common terminology criteria for adverse events version 5. National institutes of health, national cancer institute.
13. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14(2):89-103. https://doi.org/10.5114/pg.2018.81072.
14. de Kort S, Simons CC, van den Brandt PA, Goldbohm RA, Arts IC, de Bruine AP, et al. Diabetes mellitus type 2 and subsite-specific colorectal cancer risk in men and women: Results from the netherlands cohort study on diet and cancer. Eur J Gastroenterol Hepatol. 2016;28(8):896-903. https://doi.org/10.1097/meg.0000000000000626.
15. Ma Y, Yang W, Song M, Smith-Warner SA, Yang J, Li Y, et al. Type 2 diabetes and risk of colorectal cancer in two large u.S. Prospective cohorts. Br J Cancer. 2018;119(11):1436-42. https://doi.org/10.1038/s41416-018-0314-4.
16. Noh GY, Hwang DY, Choi YH, Lee YY. Effect of diabetes mellitus on outcomes of colorectal cancer. J Korean Soc Coloproctol. 2010;26(6):424-8. https://doi.org/10.3393/jksc.2010.26.6.424.
17. Cheng Y, Cheng YX, Liu XY, Kang B, Tao W, Peng D. The effect of type 2 diabetes mellitus on the short-term outcomes and prognosis of stage i-iii colorectal cancer: A propensity score matching analysis. Cancer Manag Res. 2022;14:205-14. https://doi.org/10.2147/cmar.S347242.
18. Kido H, Kato S, Funahashi K, Shibuya K, Sasaki Y, Urita Y, et al. The metabolic parameters based on volume in pet/ct are associated with clinicopathological n stage of colorectal cancer and can predict prognosis. EJNMMI Res. 2021;11(1):87. https://doi.org/10.1186/s13550-021-00831-5.
19. Zhu B, Wu X, Wu B, Pei D, Zhang L, Wei L. The relationship between diabetes and colorectal cancer prognosis: A meta-analysis based on the cohort studies. PLoS One. 2017;12(4):e0176068. https://doi.org/10.1371/journal.pone.0176068.
20. Ding J, Li C, Tang J, Yi C, Liu JY, Qiu M. Higher expression of proteins in igf/ir axes in colorectal cancer is associated with type 2 diabetes mellitus. Pathol Oncol Res. 2016;22(4):773-9. https://doi.org/10.1007/s12253-016-0065-6.
21. Argilés G, Tabernero J, Labianca R, Hochhauser D, Salazar R, Iveson T, et al. Localised colon cancer: Esmo clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(10):1291-305. https://doi.org/10.1016/j.annonc.2020.06.022.
22. Dallas NA, Xia L, Fan F, Gray MJ, Gaur P, van Buren G, 2nd, et al. Chemoresistant colorectal cancer cells, the cancer stem cell phenotype, and increased sensitivity to insulin-like growth factor-i receptor inhibition. Cancer Res. 2009;69(5):1951-7. https://doi.org/10.1158/0008-5472.Can-08-2023.
23. Caudle AS, Kim HJ, Tepper JE, O'Neil BH, Lange LA, Goldberg RM, et al. Diabetes mellitus affects response to neoadjuvant chemoradiotherapy in the management of rectal cancer. Ann Surg Oncol. 2008;15(7):1931-6. https://doi.org/10.1245/s10434-008-9873-6.
24. Uwah AN, Ackler J, Leighton JC, Jr., Pomerantz S, Tester W. The effect of diabetes on oxaliplatin-induced peripheral neuropathy. Clin Colorectal Cancer. 2012;11(4):275-9. https://doi.org/10.1016/j.clcc.2012.05.002.
25. Amshoff Y, Maskarinec G, Shvetsov YB, Raquinio PH, Grandinetti A, Setiawan VW, et al. Type 2 diabetes and colorectal cancer survival: The multiethnic cohort. Int J Cancer. 2018;143(2):263-8. https://doi.org/10.1002/ijc.31311.
26. Huang CW, Sun LC, Shih YL, Tsai HL, Chen CW, Yeh YS, et al. The impact on clinical outcome of high prevalence of diabetes mellitus in taiwanese patients with colorectal cancer. World J Surg Oncol. 2012;10:76. https://doi.org/10.1186/1477-7819-10-76.
27. Lin CY, Lin CL, Huang WT, Peng CJ, Su SB, Guo HR. Effect of diabetes mellitus comorbidity on outcomes in stages ii and iii colorectal cancer. Asia Pac J Clin Oncol. 2022;18(5):e289-e96. https://doi.org/10.1111/ajco.13639.
28. Mills KT, Bellows CF, Hoffman AE, Kelly TN, Gagliardi G. Diabetes mellitus and colorectal cancer prognosis: A meta-analysis. Dis Colon Rectum. 2013;56(11):1304-19. https://doi.org/10.1097/DCR.0b013e3182a479f9.
29. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: The cancer prevention study-ii nutrition cohort. J Clin Oncol. 2012;30(1):53-9. https://doi.org/10.1200/jco.2011.38.0303.