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Research Article

BENEFITS OF METFORMIN USE BY BREAST AND COLORECTAL CANCER PATIENTS WITH TYPE 2 DIABBETES MILLITUS: A CASE-CONTROL STUDY IN JIJEL PROVINCE (ALGERIA)

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ABSTRACT. Colorectal cancer and breast cancer are the most diagnosed cancers in Algeria. Recent studies have indicated that metformin is the first-line therapy treatment for type 2 diabetes mellitus; it may be a potential chemoprevention agent. In order to better understand the effect of metformin use on the prognosis of colorectal cancer and breast cancer in patients with type 2 diabetes mellitus, we focused mainly on the study of the tumor markers carcinoembryonic antigen and carbohydrate antigen 19-3/15-3. In this study, patients diagnosed with both colorectal cancer, breast cancer and diabetes mellitus between 2014 and 2018 were identified. Patients' clinical characteristics were analyzed for the epidemiological, case-control and survival studies in Jijel Province. We found that colorectal cancer placed in 2nd position of all cancers studied (24%), preceded by breast cancer (64%). Colorectal cancer is the most widespread cancer among digestive cancers. There was a significant decrease in serum levels of the tumor markers among the patients treated with metformin. The survival analysis for metformin users revealed that most colorectal cancer cases have been diagnosed under the age of 65 years with a female predominance. Drug combination with metformin (chemotherapy) may enhance a chemopreventive effect during the treatment of colorectal cancer and breast cancer in clinical practice. Metformin users seem to have a decreased serum carbohydrate antigen 19-3/15-3 and carcinoembryonic antigen levels compared with metformin non-users.

Keywords: *Colorectal cancer, Type 2 diabetes mellitus, metformin, tumor markers, survival.*

INTRODUCTION

According to GLOBOCAN estimates for 2018, colorectal cancer (CRC) ranks third in terms of incidence (1.8 million new cases) but second in terms of mortality (881 000 deaths), accounting for approximately 1 in 10 cancer cases and deaths worldwide [1]. In Algeria, a country with real epidemiological, demographic and nutritional transitions, the incidence of cancer is increased [2]. In 2018, the incidence of CRC was estimated at 5573 new cases representing the second most cancer in men after lung cancer, and after breast cancer (BC) in women [3]. In Jijel Province, a retrospective and descriptive study performed by Abbes and his collaborators; showed that CRC occupied the second place in relation to all cancers and the first place among digestive cancers, with a male predominance [4]. The risk of developing CRC is influenced by both lifestyle or

behavioral factors and genetically determinant factors [5]. Diabetes mellitus (DM) is one of the negative prognostic factors of cancer [6]. DM is a complex chronic systemic disease accompanied by metabolic disorders, the classification and diagnosis of which has been the subject of intense scrutiny for decades [7, 8]. DM is classified as type 1 (T1DM) and type 2 (T2DM), in which T2DM accounts for almost 95% of individuals [7]. DM is associated with an increased risk of CRC incidence and mortality in diabetic population than non-diabetic [9]. This could be attributed to several factors, including the advanced CRC among diabetic patients due to the underuse of screening. It is also suggested that diabetic patients are receiving less aggressive treatment and they are not responding as well to the treatment (chemoradiotherapy) as those without diabetes.

Another reason is that hyperinsulinemia or increased levels of insulin-like growth factors (IGF) may influence tumor aggressiveness [10]. Similarly, DM has been shown to be associated with a slightly increased risk of BC diagnosis, an increased risk of recurrence and a high risk of developing triple negative tumors [11]. Furthermore, evidence from observational studies suggests that some medications used to treat hyperglycemia are associated with either increased or reduced risk of cancer [12], such as metformin (Met), which is considered in 2016 to be the first line antidiabetic agent for T2DM [13]. Observational studies have suggested that Met may protect against the development of cancer [14], and that its use is associated with a significantly lower cancer incidence in diabetic patients [15], since Met has a positive effect on weight, reducing obesity may be beneficial for cancer risk [16].

Met may also alter cancer risk by reducing hyperinsulinemia associated with insulin resistance and increasing free circulating IGF-1 (considered as a growth factor of cancer cells), this may be sufficient to inhibit tumor growth [16]. Some researchers have indicated that Met may be a potential protective factor of colorectal adenomas and CRC in T2DM patients [17]. Thus, *in vitro* experiments have shown that Met significantly inhibits cell proliferation [18], induces cell apoptosis [19], inhibits invasive properties of cancer cells and restrains tumor growth *in vivo* [20]. In relation to BC, women diabetic patients treated with Met had a significantly lower incidence of grade III tumor, a lower incidence of triple negative and a higher incidence of estrogen receptor (ER) and progesterone receptor (PR) cancers compared to Met non-users [21].

In the present study, we are aiming to elucidate the role of Met on CRC and BC in the east region of Algeria. In order to better understand the role of Met, we focused mainly on the study of the tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-3/15-3 (CA 19-9/15-3) to examine the effect of Met use on the prognosis of CRC and BC in patients with T2DM. We also examined the association between Met use and overall survival in CRC patients.

MATERIALS AND METHODS

This was a retrospective and prospective study, conducted among CRC and BC patients at the Oncological Department of Mohammed Seddik Ben Yahia Hospital in Jijel Province. A total of 203 patients with primary invasive CRC were diagnosed between January, 2014 and December, 2018. The general population was included in the epidemiological study to establish an association between the exposure to certain factors and the occurrence of CRC. In addition, epidemiological and retrospective studies were performed with 556 patients diagnosed as BC from January 2014 to December 2018. On

the other hand, a survival analysis was conducted for three groups of CRC patients (non-diabetic, Met-users and Met non-users).

Additionally, 40 patients were selected for the case-control study of the tumor markers CEA and CA19-9 (CA 15-3) in T2DM patients treated by Met, 20 among them are affected with CRC and 20 have BC, by comparing them with non-diabetic patients whose objective is to show the protective effect of Met in cancer (Fig. 1).

Patients with colon and rectal adenocarcinomas, who received chemotherapy with XELOX and FOLFOX, and patients with CRC and T2DM, particularly those treated with Met, as well as patients with BC with the hormone receptor ER/RP expression and the HER2 protein expression were included. Any tumors other than colon and rectal adenocarcinomas, patients whose cause of death is a disease other than CRC, and the patients who died prematurely before or during treatment were excluded. The same criteria for BC were excluded.

Data were collected retrospectively from patient archived records. We recorded socio-demographic data such as age at diagnosis, year of diagnosis, gender, and clinical data (anatomopathological data) such as the topography of primary tumors. Taking into account the type and protocol of chemotherapy applied and the distribution of patients according to the number of chemotherapy sessions over the 5 years. The data obtained were presented using various descriptive statistical programs (representation in the form of histograms), processed using Microsoft Office Excel 2007. For the survival curves, data entry and analysis were performed using IBM SPSS statistics (version 27), used for Kaplan-Meier method. The survival times of patients were defined as the number of months from the date of CRC diagnosis until the last date alive (the study end date). A p-value <0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

For the epidemiological data, we sought to determine CRC and BC incidence in the population of Jijel Province. Thus, we have collected a total of 874 cancer cases identified at the level of MEB Hospital Oncology Department over the period 2014-2018 (Fig. 1). In Jijel Provence, 203 cases of CRC patients and 369 cases of patients with digestive cancers were diagnosed (Table 1). Concerning the BC, a total of 556 patients were diagnosed as BC from January 2014 to December 2018. Through these results, we found that CRC has a predominance that appears at an earlier age of between 55 and 65 years, representing 26.14% of cases with a mean age of 55 years for both sexes. We assessed the distribution of BC by sex and we found that 99% of subjects with BC were female and 1% male.

To evaluate the prevalence of type 1 and 2 DM in Jijel Provence, data on the incidence of DM in the last five years were obtained from the Directorate of Health and Population of Jijel Provence. A number of 142 and 1613 patients were considered as T1DM and T2DM, respectively (from 2014 to 2018). Among T1DM patients, the incidence of cancer is estimated to be 32.40% higher than those with T2DM. We have also noted, despite the small number of type 2 diabetics, that Met (marketed as glucophage) is the most widely used oral antidiabetic treatment. At the Oncology Department, 48 type 2 diabetic (29 females and 19 males) were estimated among CRC patients in Jijel Province and only 20 patients were Met-treated for T2DM (Table 2).

In the control case study, serum values of CEA and CA 19-9 (CA 15-3 for BC) were taken from patients' medical analysis data. The main chemotherapy regimens indicated

for these patients are FOLFOX (5-FU-oxaliplatin), XELOX (capecitabine-oxaliplatin) for CRC and taxol, CAF (cyclophosphamide, doxorubicin, 5 fluorouracil), AC-T (doxorubicin cyclophosphamide followed by docetaxel) and herceptin (trastuzumab) for BC. We selected patients who are Met-users that had received multiple sessions of chemotherapy (between 8 and 15 sessions), provided that the dates of these sessions were compatible with the dates of the medical analyses of the tumor markers. In this sense, the choice was limited (N=20; males=8 and females=12; where age ranges from 51 to 74 years) and (N=20; males=1 and females=19; with age ranging from 47 to 76 years) for CRC and BC successively, for the Met non-users population, the choice was a little bit similar (N=20; males=7 and females=13; with the same criteria of age) for the CRC; while for BC, the same criteria are chosen for the gender and the age (Fig. 2).

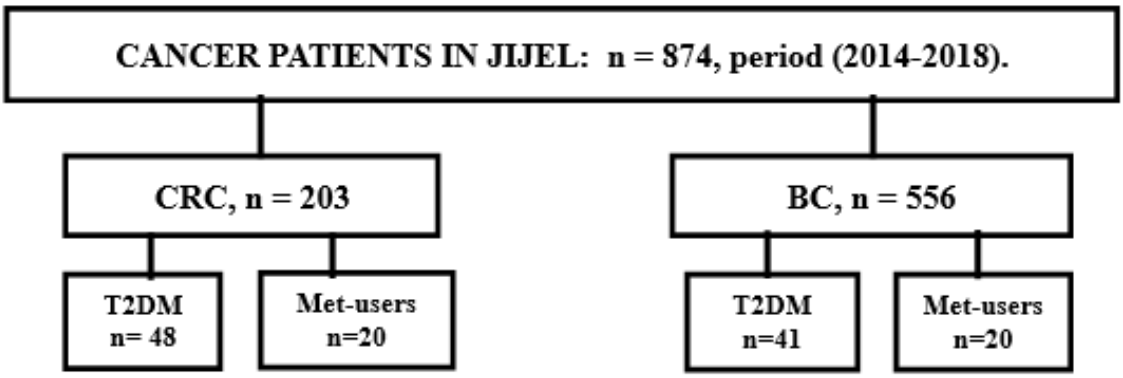

Fig. 1. *Flow diagram summarizing the process of enrolment of CRC and BC patients. BC: breast cancer; CRC: colorectal cancer; Met: metformin; T2DM: type 2 diabetes mellitus.*

Table 1. *Demographic and clinical characteristics of CRC and BC patients in the east region of Algeria. (gender, age and digestive cancer types) over the period of 2014 to 2018.*

Type of cancer	CRC (203)	BC (556)
Gender		
Female	98 (48.28%)	550 (99%)
Male	105 (51.72%)	6 (1%)
Age (years)	25-75	25-75
Anatomopathological data	Well differentiated ADK (44%) Moderately differentiated ADK (12%) Poorly differentiated ADK (8%) Undetermined 36%)	ID carcinoma (77%) IL carcinoma (12%) Rare types (11%)

BC: breast cancer; CRC: colorctal cancer; ID carcinoma: invasive ductal carcinoma; IL carcinoma: invasive lobular carcinoma.

Table 2. *Distribution of diabetic patients by type of cancer associated. The Table presents the estimated number of patients with different type of cancer in relation to diabetes (T1DM, T2DM and patients who use Met as an antidiabetic treatment).*

Types of cancer	Diabetic	T2DM	Met-users
CRC	63	48	20
BC	55	41	20
Gallbladder	5	4	1
UADT	3	3	0
Liver	4	1	0
Stomach	3	1	0
Pancreas	13	4	0
Prostate	4	2	0
Lung	4	4	0
Total	154	108	41

Met: metformin; UADT cancer: upper aerodigestive tract cancer; T2DM: type 2 diabetes mellitus

Table 3 shows the association of demographic and clinical characteristics of CRC patients with survival. In this series, we did not find significant association between survival and age at diagnosis (0.539); gender (0.813); primary tumor site (0.895) and chemotherapy as a treatment (0.33). The median survival time for age 75 and over was higher (72 months) compared to the other age groups (60 months). Patients aged over 75 years have the higher chance of survival. Of 203 CRC patients, 40 (19.70%) were diagnosed with T2DM and 20 of them were Met-users. For the three groups, most cases have been diagnosed under the age of 65 years with a female predominance, and the most common primary tumor site was the colon with well-differentiated adenocarcinomas (Table 4).

Table 5 gives the survival outcomes for non-diabetic and diabetic patients, from these results, it can be seen that there was no significant association between survival and the gender, age at diagnosis, primary tumor site and histological grade for the three groups. For the Kaplan-Meir survival analysis, of 203 CRC patients, 40 (19.70%) were diagnosed with T2DM and 20 of them were Met-users (Fig. 3).

In the first part of this study, we observed that the CRC placed in seconde position of all cancers studied (24%), preceded by BC (64%) which is quite consistent with studies reported by Abbes et al [4]. In our study, we collected 203 cases from the population of Jijel Province; 98 women (48.28%) and 105 men (51.72%). There is a slight male predominance, with a sex ratio of 1; therefore, CRC hits both men and women. The reason for this disparity is multifactorial, including eating attitudes, overweight and obesity, physical activity and sedentary behavior, race, tumor biology, late stage presentation, and variation in treatment, but access to screening and treatment is the major factors [22, 23]. There was a disparity in the incidence of CRC throughout this period as well, which should be explained by the difference in the levels of the main risk factors for CRC (obesity, physical inactivity, smoking, heavy alcohol consumption, a high-fat and/or low-fruit and vegetable diets). Globally, this increase in the incidence of CRC has been noticed in developed countries, where an upward trend is being observed. In the Maghreb countries, such as in Algeria, the trend in the incidence of CRC over the period 1996-

2010 was clearly on the rise [24, 25]. The age of the population of the region in our series was between 25 and 86 years. Patients aged less than 50 years are less likely to have CRC [26]. One of the most frequently suggested explanations for this disparity include the relative lack of access to health care among younger individuals as well as a delay in diagnosis [27].

Our results are similar to various epidemiological studies which confirm that CRC occupies the first place among digestive cancers [4], these studies are in agreement with those found in our series, where CRC represents 55% of digestive cancers. Several risk factors contribute to the development of different types of digestive cancers. Environmental and dietary factors have been shown to influence the risk of developing colorectal and stomach cancer. For CRC, there are multiple risks such as inflammatory bowel disease, colon polyp, family history of CRC, obesity and diabetes [28]. Smoking and alcohol consumption are the causal factors of the UADT cancers, and the risk increases with dose [29]. The histopathology results were presented in Table I, we observed that the well-differentiated ADKs are the majority in our series with 44%, these proportions are close to the values reported by Darré and his collaborators [30]. For both sexes combined, BC is the most commonly diagnosed cancer in Jijel Province (64%) followed by CRC (23%).

Bray et al. (2018) reported that hereditary and genetic factors, such as personal or family history of BC or ovarian cancer and inherited mutations (in BRCA1, BRCA2 and other BC susceptibility genes), represent 5-10% of BC cases [1]. In general, female patients account for 99% while almost 1% of all patients with BC occur in men. Male BC is a rare and understudied disease [31]. Biological factors, such as gender differences, hormonal regulation and response to treatment, must be taken into account when defining this disease in men [32]. BRCA mutations are among the most well-established risk factors for male BC. Population-based studies have demonstrated that 0-4% of men with BC have BRCA1 mutations and 4-16% have BRCA2 mutations [31]. We have conducted a retrospective study in which we had evaluated the values of tumor markers in relation to age groups, the human epidermal growth factor receptor-2 and hormone receptor (ER/RP) expression. The number of patients under 35 years of age with high levels of CA15-3 (1797.97 U/ml) and CEA (1374.02 ng/ml) is greater than the number of patients with low levels (2 U/ml and 0.2 ng/ml).

The same result was observed in patients over 35 years of age for high or low values of CA 15-3 and CEA. We found that there was no significant correlation between CEA and CA15-3 and age groups. These results are similar to those of Taghizadeh et al. [33]. The results obtained in our study showed significant disparities between T1DM and T2DM in the five-year period (from 2014 to 2018). They consistently demonstrate a considerable increase in the frequency of T2DM from one year to the next, reaching 381 cases in 2018. The prevalence of T2DM is progressing in parallel through a complex interplay between genetics and the environment, however, and despite the probability that genetic factors play a role in predisposition to the development of T2DM, the rapid increase in prevalence of the condition in a short time period, suggests that environmental factors play a much greater role. These include poor diet, sedentary lifestyle, smoking, air pollution exposure, physical inactivity, weight gain, and obesity [34]. T2DM is predominant in the general population of cancer patients with gallbladder cancer, UADT cancers and lung cancer. While T1DM conferred an excessive risk of pancreatic, liver and stomach cancers. Despite these values, the number of cancer incidents among T1DM seemed similar to that estimated for T2DM (46 and 108 patients respectively). This

suggests common potential mechanisms among the two populations, mentioning for example obesity, insulin treatment or diabetes-specific metabolic failures such as hyperglycemia, may provide an alternative explanation for the excessive risk of certain cancers among diabetic patients, considering that these failures are common in both types [35].

We have also noted, despite the small number of type 2 diabetics, that Met (marketed as glucophage) is the most widely used oral antidiabetic treatment. The treatment of other patients appeared to vary between sulfonylureas and thiazolidinediones (glitazones), and in some cases combined with insulin. The development of cancers, in particular pancreatic cancer, liver cancer and BC in patients with T2DM can be demonstrated by the potential role of certain antidiabetic treatments in the occurrence of cancer, which has been highlighted through epidemiological studies with large databases. It should be noted that thiazolidinediones, insulin and hypoglycemic sulfamides are able to influence CRC development [36] and, conversely, a reduction in cancer risk with Met, reinforcing the hypothesis of the role of hyperinsulinemia [37].

Recently, several observational trials are evaluating Met as a potential anti-cancer agent in patients with DM and either Met monotherapy or in combination with cytotoxic chemotherapy [38]. Furthermore, a study based on epidemiological, preclinical and clinical data has demonstrated that Met has a favorable effect on cancer proliferation markers with a reduction in cancer incidence and mortality [39].

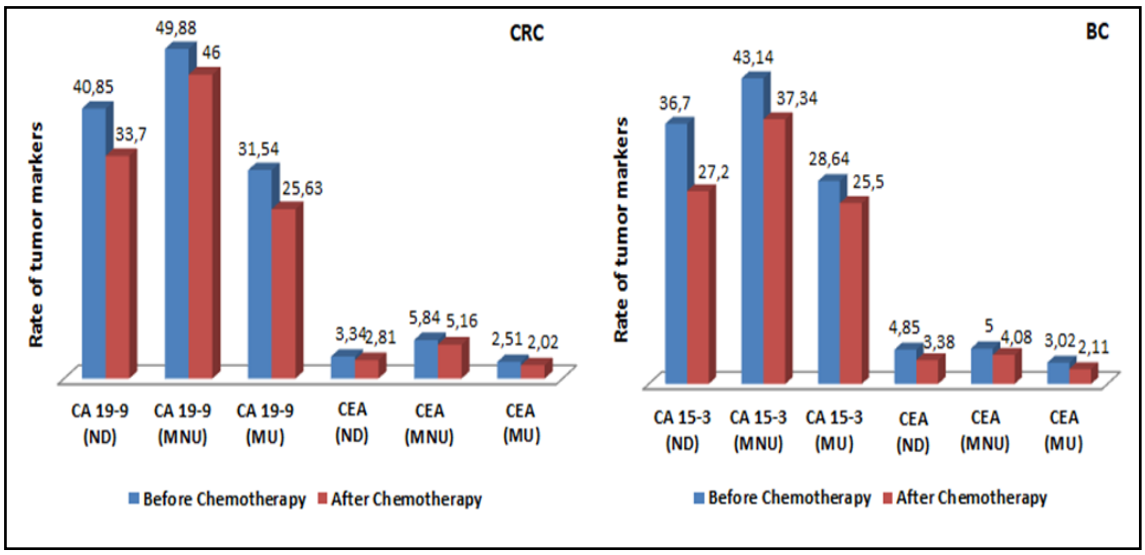

Fig. 2. *Distribution of tumor marker levels in T2DM patients with CRC and BC before and after chemotherapy. The histogram illustrates a comparison of the values of the tumor markers levels between CA 19-9, CA15-3 and CEA in three different groups (ND: non-diabetic, MNU: Met non-users and MU: Met-users).*

Table 3*. Association of demographic and clinical characteristics of CRC patients with survival using log rank test.*

Parameters	Frequency (N,%)	Median (95% CI) (months)	p-value
Age groups			
<65	(59%)	60 (50.9-69.1)	
65-75	29 (29%)	60 (44.1-75.9)	0.539
>75	12 (12%)	72 (53.7-90.3)	
Gender			
Male	58 (58%)	60 (51.5-68.5)	0.813
Female	42 (42%)	48 (40-56)	
Primary tumor site			
Colon	13 (13%)	60 (42-78)	
Left colon	13 (13%)	48 (31-65)	
Right colon	12 (12%)	36 (15.6-56.4)	
Sigmoid colon	24 (24%)	60 (48.5-71.5)	0.895
Transverse colon	4 (4%)	48	
Rectum	13 (13%)	60 (49.5-70.5)	
Upper rectum	6 (6%)	36 (22.4-49.6)	
Distal rectum	15 (15%)	48 (41.2-54.8)	
Chemotherapy			
XELOX	68 (68%)	48 (40.4-55.6)	0.33
FOLFOX	32 (32%)	60 (50.9-69.1)	

N: nomber of cases; CI: confidence interval

The association among T2DM, Met and CRC has been investigated to examine whether Met would affect the prognosis of CRC patients with T2DM, by studying the correlation between the therapeutic response of Met and the risk of CRC based on the evaluation of CEA and CA 19-9 serum levels in Met -treated TADM patients compared to non-diabetic patients. Serum values of CEA and CA 19-9 (CA 15-3 for BC) were taken from patients' medical analysis data, with the understanding that the concentration of CEA is considered as normal when it is less than 5 µg/l, while that of CA 19-9 (CA 15-3) should be less than 37-39 U/ml [40,41]. In addition, we performed the same association with BC patients to show the protective effect of Met, as it has been suggested in various studies that the use of Met may have an anti-tumor activity against several molecular subtypes of BC, as well as inhibiting cell growth, colony formation and inducing cell cycle arrest *in vitro* [42].

Table 4. *The general characteristics of the non-diabetic and diabetic patients, comparing those of the Met-users with Met non-users.*

Patients	**Non-diabetic (100)**	**Diabetic (40)**	
		***Met-users* (20)**	***Met non-users* (20)**
Parameters	**N(%)**	**N(%)**	**N(%)**
Gender			
Male	42 (42%)	8 (40%)	7 (35%)
Female	58 (58%)	12 (60%)	13 (65%)
Age groups			
<65	59 (59%)	10 (50%)	10 (50%)
65-75	29 (29%)	10 (50%)	8 (40%)
>75	12 (12%)	0	2 (10%)
Primary tumor site			
Colon	66 (66%)	19 (95%)	16 (80%)
Rectum	34 (34%)	1(5%)	4 (40%)
Histological grade			
Well differentiated	82 (82%)	10 (50%)	14 (70%)
Moderately differentiated	10 (10%)	5 (25%)	2 (10%)
Poorly differentiated	8 (8%)	5 (25%)	4 (20%)

Met: metformin; N: number of cases

Before chemotherapy, the results obtained indicate a significantly high CEA and CA 19-9 with Met. This result may be a strong suggestive of metastatic colorectal adenocarcinoma, due to the increased level of CA 19-9 that is associated with more advanced CRC, which can be used as a marker in addition to CEA without an increase in its level in CRC patients [43]. 45% of the patients had variation in CEA and CA 19-9 levels within the normal reference ranges, similarly for control patients. This is explained by the fact that these markers have a low ability to detect primary CRC mainly due to low sensitivity in the early stage of the disease. However, one of the major limitations of CEA is that 20-30% of patients with CRC do not produce elevated serum levels despite the presence of an advanced cancer. That is why it is necessary to evaluate other markers; in particular CA 19-9 [44, 45]. In this situation, more analysis is required to confirm the presence of malignancy and to locate the tumor site. Due to the normal tumor marker values before chemotherapy in patients treated with Met, this suggested that Met is likely to be chemopreventive in the early stages of colorectal adenocarcinoma. This suggestion is similar to the results of the study carried out by Hou et al. [46].

Table 5. *Comparison of survival outcomes for non-diabetic and diabetic patient, using log rank test, the survival outcomes (mean, median and p-value) for non-diabetic and diabetic patients including metformin users.*

Parameters	**Age (months)**		**p-value**			
Patients	Mean (95% CI)	Median (95% CI)	Gender	Age groups	PTS	HG
Non-diabetic	65.45(50.6-80.3)	60 (54-66)	0.813	0.539	0.725	0.661
Diabetic Met users	54.5 (43.2-65.8)	60 (35.6-84.4)	0.65	0.96	0.220	0.47
Diabetic Met non users	52 (37.4-66.7)	48 (29.3-66.7)	0.516	0.7	0.524	0.352

Met: metformin; PTS: primary tumor site; HG: histological grade

After chemotherapy, and based on the results shown in (Fig. 2); there was a significant increase in serum levels of the tumor markers among the patients treated with Met. Returning to the medical tests of patients treated with Met, we noted that the levels of their tumor markers throughout the period of chemotherapy (from 8 months to 15 months) have normal values. In this case we can affirm the result obtained by Peng and his collaborators, that the combination of Met with chemotherapeutic drugs reveals a powerful synergistic efficacy to treat different cancers by molecular mechanisms [47]. A recent research based on the combination of Met with 5-FU, has found that Met can reverse the resistance of tumor cells and the inhibition of their proliferation synergistically. It has also targeted cancer stem cells and suppressed the expression of hypoxia-inducible factors in some digestive cancers [48, 49]. Nevertheless, after the patients had stopped chemotherapy completely (from more than a few months to 4 years), we found that the values did not change any more, they remained normal to moderately stable (Fig. 2), which indeed allows us to conclude that Met had a protective effect and increased their survival. These results are similar to those shown in the study conducted by Kanadiya et al [50]. Another study carried out by Deng et al. (2019) reported that higher doses or longer durations of Met have an effective antitumor activity in T2DM patients; it has also a protective effect against colorectal adenoma initiation, malignant transformation and progression independent of its hypoglycemic effect [51]. Several studies have investigated the association between BC risk and T2DM [52].

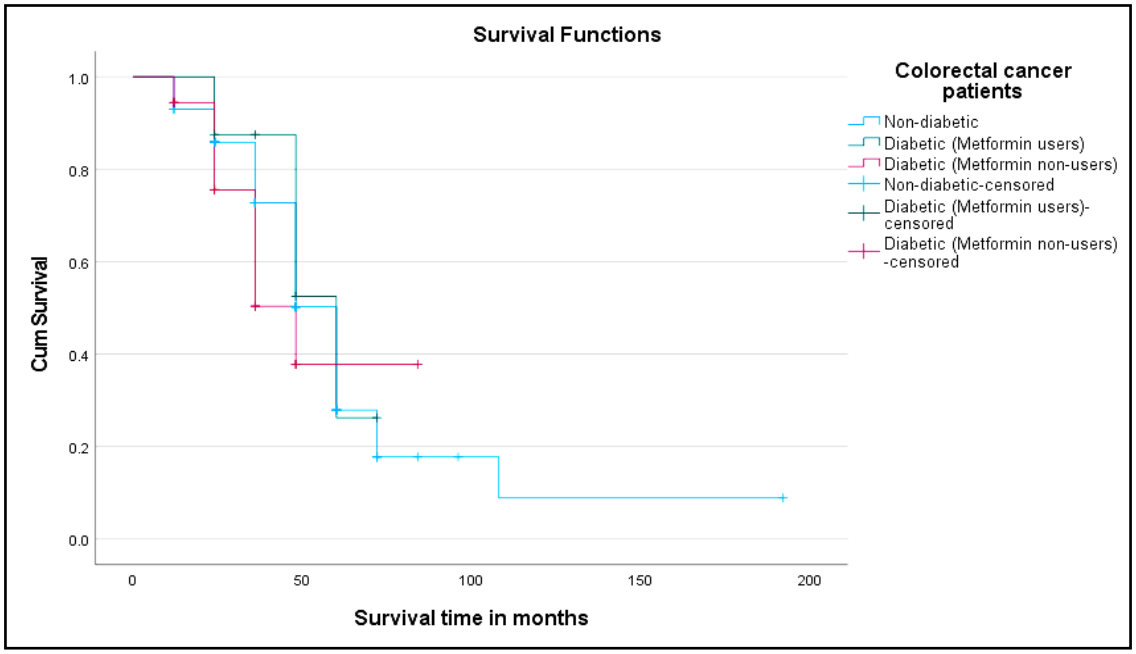

Fig. 3. *Kaplan-Meier curve comparing the overall median survival between non-diabetic and diabetic (Met-users/non-users) patients.*

In a study of nurses' health, data indicated that women with T2DM have an increased risk of developing BC than women with no diabetes. Moreover, in a recent systematic review and meta-analysis, it was observed that protective effect of Met for all cause mortality in patients with T2DM and BC [54]. So, we have conducted a supplementary case-control analysis among type 2 diabetic BC patients that is similar to the study investigating with CRC patients, by evaluating the CEA and CA 15-3 serum levels in Met -treated T2DM patients compared to non-diabetic patients. Before chemotherapy, marker levels of CEA and CA 15-3 in both Met-users and non-users are at normal values (Fig. 2). Elevated levels of CA 15-3 are found in the majority of BC patients with distant metastasis, high concentration may also occur in patients with several different types of advanced adenocarcinoma [55]. During chemotherapy, the levels of CEA and CA 15-3 decrease progressively in both populations, bearing in mind that studies on the anti-tumor effect of Met in metastatic cancer stages are not yet available. On the other hand, results for other patients during and after chemotherapy for both Met users and non-users remained normal to moderately stable (Fig. 2), concluding that Met (not combined or combined with chemotherapy) decreases BC tumor progression [56]. To confirm that Met can be used as an adjuvant to chemotherapy in BC, Jiralerspong and colleagues showed that treatment with Met improves the response rate (defined as an absence of tumor in the tissue removed during surgery) in BC patients treated with neoadjuvant chemotherapy. This effect was particularly clear in diabetic women treated with Met compared to those who were not [57].

For the Kaplan-Meir survival analysis, for the three groups, most cases have been diagnosed under the age of 65 years with a female predominance, and the most common primary tumor site was the colon with well-differentiated adenocarcinomas (Table 3). The possible differences between women and men in our population, exactly in diabetics, are related to potential gender differences in the use of Met and the degree of glucose control. Women generally have a tendency to have better glucose control than men [58,

59]. Table 4 and 5 give the survival outcomes for non-diabetic and diabetic patients, from these results, it can be seen that there was no significant association between survival and gender, age at diagnosis, primary tumor site and histological grade for the three groups. In diabetic patients' group, the estimated mean and median for survival time for Met-users were higher compared to Met non-users but we did not find a significant result concerning survival analysis for the Met-users group; this is due to the small number of patients included in this study (Fig. 3). A retrospective analysis conducted by Garrett and his collaborators, has shown that the use of Met in CRC patients was associated with an improved overall survival [60]. Other cohort studies have demonstrated that the use of Met in CRC patients is associated with a reduced mortality when compared to diabetic patients who did not take Met. Met-users had only a 10% increase in mortality rate over non-diabetic CRC patients, whereas diabetic patients treated with diabetic treatments other than Met experienced a 22% increase [61, 62]. Based upon these observations; we have demonstrated a higher correlation between the effect of Met and CRC. One potential biological mechanism linking diabetes and CRC includes the state of insulin resistance/hyperinsulinemia, which stimulates the IGF pathway, and in turn may promote tumor cell proliferation and angiogenesis [63]. Hyperglycemia itself and resulting oxidative stress, accumulation of advanced glycation end products, and chronic inflammation may enhance malignant transformation, cancer cell proliferation, metastasis, perineural invasion, and chemotherapy resistance, and inhibit apoptosis [64, 65].

CONCLUSION

Our results have indicated that Met use seems to be an effective anticancer drug in relation to CRC and BC. Met is associated with a decreased serum levels of CA 19-9, CA 15-3 and CEA in CRC and BC patients with T2DM. This appreciative effect on the tumor markers could be used to control the disease process in patients with CRC and BC. However, drug combination with Met (chemotherapy) may enhance a chemopreventive effect during the treatment of CRC and BC in clinical practice. For the survival analysis, there is no significant association between Met and CRC patients in our population but, many studies showed a real association between the effect of Met and survival in diabetic CRC patient. Future studies will be needed to evaluate the potential of Met as a preventive molecule for CRC patients with T2DM. The screening program appears to lead for an earlier detection and a better prognosis. We unfortunately found a lack of the early detection program since patients did not receive a colonoscopy until after signs of tumor presence had appeared. Evidently, future *in vivo* studies would have been expanded to deepen our findings regarding the protective effect of Met and its contribution in improving the survival of CRC patients.

In this work, we tried to prove and understand the association between Met and improved survival in diabetic CRC patients and add to a foundation of evidence supporting the anticancer effects of Met. Future prospective studies will be needed to confirm that Met has a real effect on the survival of CRC patients with T2DM with a big number of diabetic CRC patients.

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Conflict of Interest. The authors declared that there is no conflict of interest.

Authorship Contributions. Arbia ABBES designed the study, analyzed the data, interpreted the results and wrote the manuscript. Rihab BOUDEMIA collected the data and participated in the study design and data analysis. Hocine RECHRECHE funded the project, supervised and revised the manuscript. All authors participated in the review and editing of the final manuscript.

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