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Role of Metformin in Enhancing Response to Neoadjuvant Chemo-Radiotherapy in Patients with Locally Advanced Rectal Carcinoma

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Abstract

Background: Metformin may improve response to concomitant chemoradiotherapy (CCRT) in treatment of locally advanced rectal carcinoma. We aimed at evaluating the potential impact of metformin on pathologic complete response (pCR) of rectal cancer cells to CCRT indiabetic patients; (2) Methods: A total of 50 diabetic patients with locally advanced rectal carcinomawere treated with neoadjuvant CCRT followed by surgery from June 2018 to June 2020. Patients were divided into metformin group (n = 25) and non metformin group (n = 25). Tumor response was compared between the two groups. Tumor response was also compared in relation to multiple predictive factors; (3) Results: The rates of pCR was significantly higher in metformin group (p = 0.025). The rates of pCR was also significantly higher in patients who had BMI <30 kg/m^2 (p = 0.021), pre treatment blood glucose level <200mg/dL(p = 0.005), and interval of radiotherapy to surgey≤8 weeks (p = 0.001); (4) Conclusions: Metformin use is associated with a significant increase in pathological complete response rates to concomitant chemoradiotherapy in diabetic patients with locally advanced rectal cancer.

KeywordsRectal cancer . Metformin . Radiotherapy. Tumor response . Diabetes.

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Data have been used in a secondary analysis including a large number of diabetic and non diabetic patients.

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Introduction

Colorectal cancer (CRC) is the third most incident cancer and the fourth cause of death by cancer in the world [1].Neoadjuvant combined chemo-radiotherapy followed by surgery and adjuvant chemotherapy, is considered the current standard treatment for stage III rectal cancer [2].

Recent evidence suggests that patients who achieved a complete pathological response after neoadjuvant chemo-radiotherapy, have a more favorable outcome than patients with incomplete pathologic response [3].A retrospective study has showed that carcinoembryonic antigen (CEA) before chemo-radiotherapy (CRT), tumor (T) stage before CRT, interval between the end of CRT and surgery, and maximum depth of tumor invasion before CRT had a significant influence on pCR [4].

Diabetes mellitus and hyperinsulinemia may increase the risk of colorectal neoplasia by different mechanisms [5]. Metformin is considered the first-line drug used for the standard treatment of type 2 diabetes mellitus [6]. In addition, Metformin could be used as an antiaging agent [7], a cardiac protective agent [8], a neuroprotective agent [9], or as an optional agent for treatment of polycystic ovarian syndrome [10]. Furthermore, there is growing interest in metformin's potential benefits in cancer. Metformin may reduce the risk and mortality of cancer and improve the response of cancer cells to therapy [11, 12]. Overall, incidence and mortality of cancer were decreased by 10%-40% in patients with diabetes, who received metformin doses of 1500–2250 mg/day. Recently, numerous studies have been emerged to determine whether a similar effect can be shown in non diabetic cancer patients [13, 14, 15].

However, metformin can cause multiple adverse effects. The gastrointestinal adverse effects are more common with metformin than other hypoglycemic medications. These gastrointestinal adverse effects include diarrhea, vomiting, flatulence and nausea [16]. Lactic acidosis is rare but most serious adverse effect and the majority of cases is related to impaired kidney and liver functions [17].

We aimed at evaluating the potential impact of metformin on pathologic complete response (pCR) of rectal cancer cells to CCRT indiabetic patients.

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Patients and Methods

i.Patients

A total of 50 diabetic patients with locally advanced rectal cancer were treated with neoadjuvant CCRT followed by surgical resection from June 2018 to June 2020. All patients had histologically confirmed primary adenocarcinoma with a clinically T3–T4 and/or node-positive rectal cancer located <15 cm from the anal verge. Clinical TNM stage prior to neoadjuvant CCRT (cTNM) was assessed radiologically using colonoscopy, endorectal ultrasonography, abdominopelvic CT, pelvic MRI, or PET. Patients with synchronous malignancies, recurrent disease, distant metastases, previous treatment for cancer and non diabetic patients, were excluded from the study.Age, gender and body mass index (BMI), were obtained from the patient's chart or pharmacy record.This study has been approved by the Ethical Committee of the Department of Clinical Oncology, Faculty of Medicine, Ain Shams University.

ii.Methods

Antidiabetic medications were identified through patient's medical records. Patients were divided into two groups: 25 patients received metformin (metformin group) and 25 patients received other antidiabetic medications (non metformin group). Laboratory findings including pretreatment serum carcino-embryonic antigen (CEA), blood glucose, HbA1c percentage, and arterial blood gases within 1 month prior to treatment were recorded for all patients.

All patients received radiotherapy that consisted of 1.8–2.0 Gy daily fractions for a total dose of 54 Gy. Either capecitabine (825 mg/m2/day) twice daily during radiotherapy or intravenous 5-FU (425 mg/m2/day) and calcium leucovorin (20 mg/m2/day) for 5 days at the first and fifth weeks of radiotherapy, was received during radiotherapy. All patients had surgery between 6 and 12 weeks after the completion of neoadjuvant CCRT.

TNM stage was defined according to the Cancer Staging Manual Seventh Edition by the American Joint Committee on Cancer. Tumor response to radiotherapy was assessed by pathologic complete response (pCR). Tumour grade and pathologic response were determined in the surgical specimen by the pathologist at the time of surgical resection. Pathological complete response was defined as the absence of viable tumor cells in both the primary site and dissected lymph nodes. The primary endpoint of this study was pathological complete response (pCR)to concomitant chemoradiotherapy associated with metformin use.

iii.Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 20.0; IBM SPSS Statistics, IBM Corporation, Armonk, NY). Patient characteristics were compared between groups using Chi-square, Fisher's exact test, or linear-by-linear association. Univariate analysis of pCR rates was performed using logistic regression, with the following variables included: metformin use, age, BMI, pretreatment CEA, blood glucose level, and HbA1c level,clinical tumor and nodal stage, tumor distance from anal verge, circumferential extent, tumor grade, and interval of radiotherapy to surgery. Multivariate analysis of pCR rates was performed through comparing patients receiving metformin regimens and patients not receiving metformin regimens. Quantitative data will be presented as median and standard

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deviation and t-test for independent samples will be used to compare the two groups. Qualitative data will be presented as number and appropriate percent and chi-square test will be used to compare proportions across the different groups. Value of less than or equal to 0.05 will be considered significant. SPSS version 20 will be used for data entry, presentations and analysis of the data.

Results

Patient characteristics

A total of 50 diabetic patients with locally advanced rectal cancer were treated with neoadjuvantCCRT followed by surgical resection from June 2018 to June 2020. Of the 50 patients, 25 were in a metformin group and 25 were in a non-metformin group. Metformin was prescribed in a dose of 250 mg once to 850 mg three times per day. All patients and disease characteristics of the study group were summarized in table1.

Table 1: Patients and disease characteristics of the study group.

Patient demographics	**All patients (*n* = 50)**	**Metformin group**	**Non metformin group**	***p* value**
Age, year	52.7 (39-77)	58(41-75)	52.7(39-77)	0.787
Gender, n (%)				
Male	36 (72%)	21(84%)	15(60%)	0.114
Female	14(28%)	4(16%)	10(40%)	
BMI, kg/m2	30.3 (17-46)	32.4(17-46)	28.3(17-42	0.104
Blood glucose, mg/dL	157.4 (84-284)	165.5 (84-284)	149.4 (85-248)	0.230
HbA1c, %	5.8 (5.1-6.6)	5.7 (5-6.2)	5.9 (5.2-7.1)	0.162
CEA, ng/mL	1.9 (1.1-7.2)	1.9 (1.3-7.2)	1.7 (1.1-7.6)	0.808
Distance from anal verge, cm	4.5 (3.5-5.5)	5 (3.9-6.8)	4.5 (3.5-5.1)	0.390
Circumferential extent, %	64.1 (31-85)	62.4 (31-85)	65.7 (52-84)	0.329
Clinical T stage, n (%)				
T2	1 (2%)	1(4%)	0(0%)	0.165
T3	41(82%)	18(72%)	23(92%)	
T4	8(16%)	6(24%)	2(8%)	
Clinical N stage, n (%)				
N0	2(4%)	2(8%)	0(0%)	0.019
N1	29(58%)	18(72%)	11(44%)	
N2	19(38%)	5(20%)	14(56%)	
Differentiation				
WD	2(4%)	1(4%)	1(4%)	
MD	43(86%)	21(84%)	22(88%)	0.796
PD	4(8%)	2(8%)	2(8%)	
Unknown	1(2%)	1(4%)	0(0%)	
Concurrent chemotherapy				
Capecitabine	32(64%)	18(72%)	14(56%)	0.243
5-FU	18(36%)	7(28%)	11(44%)	
Interval to surgery, weeks (range)				0.172
Median	8 (6-12)	9 (6-12)	7.5 (6-11)	
Surgical procedure, n (%)				
LAR	7(14%)	5(2%)	2(8%)	0.143
APR	41 (82%)	18 (72%)	23 (92%)	
Unknown	2 (4%)	2 (8%)	0 (0%)	
Adjuvant chemotherapy, n (%)	24(48%) 20 (40%)	14(56%) 9 (36%)	10(40%) 11 (44%)	0.465

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Capecitabine 5FU No adjuvant chemotherapy	6(12%)	2 (8%)	4 (16%)	

APR abdominoperineal resection, BMI body mass index, CEA carcinoembryonic antigen, 5-FU 5fluorouracil, LAR low anterior resection, MD moderately differentiated, PD poorly differentiated, WD well differentiated.

Tumor response and metformin use

Pathologic tumor response was assessed, but survival analysis was not conducted because of the short follow-up duration. Analysis of pCR was performed to assess pathologic tumor response. The rate of pCR was significantly higher in the metformin group (44 %) than in the non-metformin group (12%) (p = 0.025) (Figure1). However, metformin dose was not significant factor for pCR.

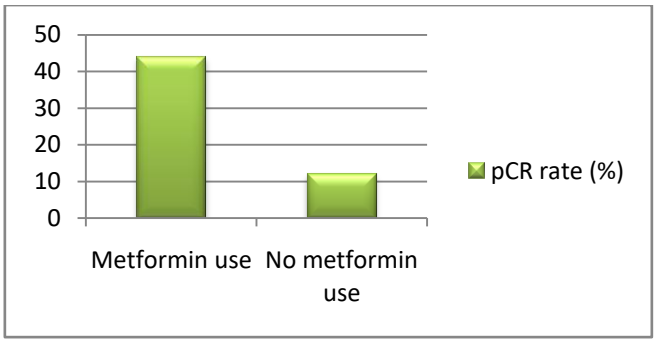

Figure 1: pCR& metformin.

Tumor response and other variables

BMI (p = 0.021), pretreatment blood glucose (p = 0.005) and interval of surgery (p = 0.001) were also associated with high rate of pCR (Figure 2, 3, 4). However, patients age, pretreatment HbA1c and CEA levels were not significant factors for pCR. In addition, when we evaluated whether pCR was different according to distance of tumors from anal verge, circumferential extent of tumors, clinical tumor stage and clinical nodal stage, no significant differences were observed. Correlation between pCR in treatment groups and multiple predictive factors is shown in table2.

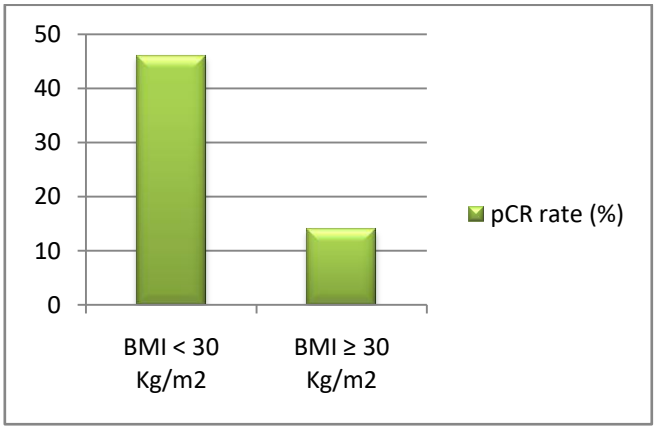

Figure 2: pCR& BMI.

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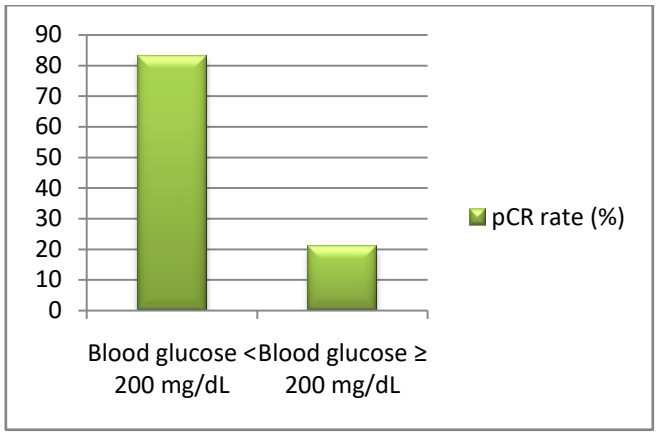

Figure 3: pCR& non fasting blood glucose level.

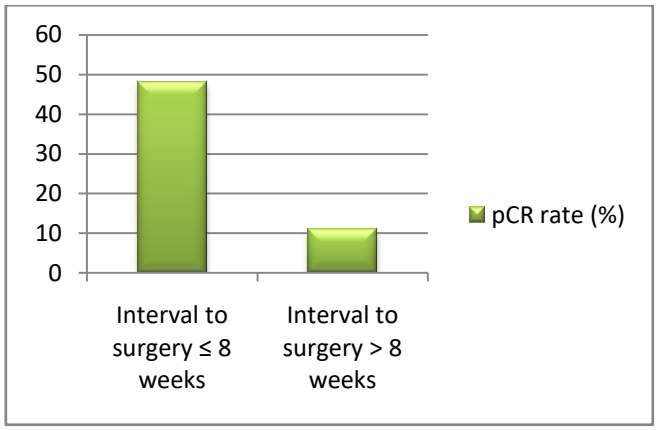

Figure 4: pCR& interval to surgery.

Table 2: Pathological complete response in treatment groups and its correlation with multiple predictive factors

	Total number	**PCR *n* (%)**	**Pvalue**
All patients	**50**	**14 (28)**	
Metformin group	25	11 (44)	0.025*
Non metformin group	25	3 (12)	
Metformin Dose, mg:			
250 once-<500 bid	2	0 (0)	0.206
500 bid	19	8 (42)	
>500 bid – 850 tqd	4	3 (75)	
Age, years			
<60	29	8 (28)	0.940
≥60	21	6 (29)	
BMI, Kg/m^2			
<30	22	10 (46)	0.021 *
≥30	28	4 (14)	
Blood glucose, mg/dL			
<200	6	5 (83)	0.005*
≥200	44	9 (21)	
HbA1c, %			
<6.5	37	12 (32)	0.303
≥6.5	13	2 (15)	

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CEA, ng/dL			
<2.2	32	8 (25)	0.533
≥2.2	18	6 (33)	
Distance from anal verge (range), cm			
≥6	9	5 (56)	0.094
<6	41	9 (22)	
Circumferential invasion, %			
<50	4	3 (75)	0.061
≥50	46	11 (24)	
Clinicaltumour stage:			
T2-3	42	10 (24)	0.197
T4	8	4 (50)	
Clinical nodal stage:			
N0	2	2 (100)	0.074
N1-2	48	12 (25)	
Differentiation			
WD	2	2 (100)	
MD	43	11 (26)	0.129
PD	4	1 (25)	
unknown	1	0 (0)	
Interval to surgery, weeks			
≤8	23	11 (48)	0.001*
>8	27	3 (11)	

BMI body mass index, CEA carcino-embryonic antigen, MD moderately differentiated, pCR pathological complete response, PD poorly differentiated, WD well differentiated.

Discussion

Metformin, beyond its role in affecting the patient's diabetic state, has received attention since recent studies suggested that it can improve the response to therapy in esophageal cancer [18], prostate cancer [19], and breast cancer patients [20, 21].

Recently, otherstudies showed the metformin impact on pCR and survival in rectal cancer patients [22, 23]. The administration of metformin hydrochloride stimulates activation of AMPK and inhibits phosphorylation of acetyl-CoA carboxylase resulting in inhibition of the mammalian target of rapamycin (mTOR) pathway. As a result, colonic epithelial proliferation is suppressed [24, 25]. One prospective large clinical study showed that the metformin use significantly decreased the risk of colorectal neoplasia by decreasing the number of crypt foci [22].Zhang et al studied the synergistic effect of metformin hydrochloride and 5-Flurouracil (5-FU) on the apoptosis of CD133+ stem cells of human colorectal cancer cell lines [26]. Furthermore, administration of metformin with vitamin D, exhibited synergistic effects on prevention of the developing early colon neoplasia [27].

The aim of our study was the assessment of the metformin impact on pCR rates after concomitant chemo-radiotherapy in patients who had diabetes and rectal cancer with locally advanced stage through comparing between patients receiving metformin containing regimens and patients receiving other hypoglycemic regimens.

In our study,14 patients (28%) had pCR whilein Skinner et al study,80 patients (17%) of the 482 patients, had pCR [22]. Metforminhad a significant impact on pCR in our study (P = 0.025) and in Skinner et al study (P = 0.02).In contrast, in Kim et al study, metformin use did not have significant impact on pCR (P = 0.293) [22, 23].

The age had an insignificant impact on pCR in our study and Skinner et al study (P = 0.940,

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0.2 respectively). However, Kim et al study reviewed that agewas associated with significant impact on pCR (P = 0.037) [22, 23].
Given the fact that obesity can be associated with inflammation and angiogenesis [28], and is associated with the chronic oxidative stress [29], it is possible to consider the possibility that obesity is related to the response of radiotherapy. However, few previous studies reported the significance of obesity in predicting pCR after neoadjuvant CCRT in rectal cancer [30]. In our study, the BMI had a significant impact on pCR (P = 0.021) while it had an insignificant impact in Skinner e al study (P = 0.43) [22].

Rectal cancer patients with diabetes have worse prognosis than non diabetic patients. One study showed that the pCR was significantly higher in nondiabetic patients, and was not achieved in any of diabetic patients [31]. In our study, the serum non fasting pretreatment blood glucose level had a significant impact on pCR (P = 0.005) while it had an insignificant impact in Skinner et al study (P = 0.6) [22]. Furthermore, the serum pretreatment CEA level had an insignificant impact on pCR (P = 0.533) compared to its significant impact in Skinner et al study (P = 0.05) [22].
Our study was performed by a small number of institutions and included a small number of diabetic patients that was not sufficient to obtain significant results, though we included all patients who had inclusion criteria of this study. Non diabetic patients were not included in this study in comparison to Kim et al and Skinner et al studies. This study assessed tumor response by pCR while Kim et al study assessed tumor response by pCR, T-downstaging, N-downstaging and tumor regression grade. Kim et al study also evaluated impact of metformin on 4-year DFS rates and OS rates, LRC rates and time to DM rates [22, 23].

Our study supported the hypothesis that metformin use increases pCR in rectal cancer and this seems to be consistent with a radiosensitization efficacy of metformin which was observed in other diseases. Further studies are needed to be carried out on a larger number of rectal cancer patients including diabetics and non diabetics. Also, further prospective trials for identifying the mechanism of metformin as a radiosensitizer, would facilitate the clinical application of metformin in the treatment of stage III rectal cancer.

Author contributions

EmanElsayed, Atef Youssef Riad, Dina Ahmed Salem and DiaaEldinMoussa designed the study, EmanElsayed performed data collection and analysis, EmanElsayed wrote the manuscript. All authors were involved in the revision of the manuscript.

Conflict of Interest: none

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Figure Legends

Figure S1: pCR& metformin.
Figure S2: pCR& BMI.
Figure S3: pCR& non fasting blood glucose level.
Figure S4: pCR& interval to surgery.

Abbreviation list

APR : Abdominoperineal resection.

BMI : Body mass index.

CEA : Carcinoembryonic antigen.

CRC : Colorectal cancer.

CRT : Chemo-radiotherapy.

DRE : Digital rectal examination.

5-FU :5-Flurouracil.

LAR : low anterior resection.

MD : moderately differentiated.

PCR : Pathological complete response.

PD : poorly differentiated.

T : Tumor size.

WD : well differentiated.