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Association between diabetes and oncological outcomes in patients undergoing neoadjuvant chemo-radiotherapy for rectal cancer

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ABSTRACT

Purpose: The aim of the study was to investigate, in a nationwide study, if diabetes and especially metformin exposure during neoadjuvant chemo-radiotherapy improves the oncological outcomes in patients with rectal cancer.

Methods and materials: Patients undergoing neoadjuvant chemo-radiotherapy and curative intended resection for rectal cancer in Denmark between January 1, 2003 and July 1, 2015 were identified. Diabetes was defined as medically treated diabetes. Only patients who were either active users of antidiabetic medication at the beginning of the radiotherapy or never-users were included. Active users were matched with never-users 1:2 by propensity score. Subgroup analyses concerning metformin treatment were performed. The primary outcome of the study was disease-free survival and the secondary outcomes were recurrence free survival and all-cause mortality.

Results: A total of 9799 patients were undergoing rectal cancer surgery with curative intend in the period. Of those, 2379 received neoadjuvant treatment up to one year preceding surgery. In total 459 patients were included in the study 154 patients with diabetes and 305 not diagnosed with diabetes. In the diabetes group, 53 were in active treatment with metformin. No statistical difference between the diabetes group and the non-diabetes group was shown with respect to disease free survival (HR 0.96, 95%CI 0.73–1.26, p = 0.77), recurrence-free survival (HR = 1.11, 95% CI 0.78–1.58, p = 0.56) or all-cause mortality (HR = 0.94, 95% CI 0.69–1.28, p = 0.69). Metformin treatment did not influence any of the outcomes.

Conclusion: Our study does not support that diabetes or metformin use are associated with response to neoadjuvant chemo-radiotherapy in terms of disease-free survival, recurrence-free survival or all-cause mortality.

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide. Surgical removal of the tumor is the only curative treatment, but still 30–40% of patients with potentially curable CRC relapses [1]. Diabetes mellitus and colorectal cancer share several risk factors including obesity and physical inactivity, and diabetes is proven to be an independent risk factor for developing colorectal cancer [2].

Metformin is the drug of choice for treatment of type 2 diabetes, and several studies indicate that metformin-users may both have a decreased risk of developing certain cancers including colorectal cancer [3–5] and have potential survival benefits [4,6–12]. The antineoplastic molecular action of metformin is believed to work through the inhibition of the mammalian target of the rapamycin (mTOR) pathway [13]. This pathway has a central role in regulating basic cell behaviors such as regulation of protein synthesis and cell growth as well as cell survival, metabolism, and cytoskeletal organization [14–16]. Studies show that metformin has an antineoplastic effect and can inhibit cancer cell growth [13,17].

The standard treatment for locally advanced rectal cancer is neoadjuvant chemo-radiotherapy followed by total mesorectal excision. This improves resectability, achieves better chance of sphincter preservation and reduces the risk of local recurrence [18–20]. Tumor response to neoadjuvant radiotherapy is an important factor for local recurrence and survival, and the presence of tumor hypoxia is a negative prognostic factor. It has been suggested that patients with diabetes have lower response to neoadjuvant chemo-radiotherapy than non-diabetes patients. These studies have, however, been limited by small

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sample sizes and lack of long-term outcomes [21,22]. Besides the suspected antineoplastic effects exerted through the mTOR pathway, metformin directly inhibits the complex I activity in the mitochondrial electron transport chain. This could lead to an increase in the response to radiotherapy through inhibition of tumor cell oxygen consumption and improved tumor oxygenation [23]. This is supported by studies suggesting that patients with metformin-treated diabetes have improved response rates for radiotherapy in several malignancies [23] Only a few studies have investigated the radio sensitizing effect of metformin in rectal cancer [24,25].

The aim of the study was to investigate, in a nationwide study, if diabetes and especially metformin use during neoadjuvant chemo-radiotherapy affects the oncological outcomes in patients with rectal cancer.

2. Methods

Through the national clinical register of the Danish Colorectal Cancer Group (DCCG), patients undergoing neoadjuvant chemo-radiotherapy and curative intended resection for rectal cancer in Denmark between January 1, 2003 and July 1, 2015 were identified.

The DCCG includes 98.6% of all patients diagnosed with colorectal cancer and contains detailed information regarding demographic factors, comorbidity, and peri- and postoperative treatment [26]. In the Danish National Patient Register (NPR) all hospital contacts including outpatient visits are registered [27]. Information regarding hospital admission such as date of admission and discharge, procedure codes and diagnoses was obtained from the NPR. A unique personal identification number (CPR-number) is assigned to all Danish residents and information on immigration, emigration, and mortality among all residents are recorded in the Danish Civil Registration System. This system is complete, and loss to follow up is minimal [28]. The unique CPR-number makes it possible to link the registers used. The Danish Pathology Register (DPR) [29] have recorded standard data on biological specimens and coded these using the Danish version of the Systemized Nomenclature of Medicine (SNOMED). SNOMED codes can be used to document pathological diagnosed recurrences. All incident cancer cases in the Danish population since 1943 are registered in The Danish Cancer Registry (DCR) [30]. The study population was linked to the DCR in order to be able to identify patients with a history of cancer. Since 1995, prescribed drugs dispensed at the Danish community pharmacies have been registered in the Danish National Prescription Registry (DNPR) [31]. All redeemed prescriptions, including WHO defined daily doses (DDD) and date of dispensing, were identified. Indication and prescribed dose are not recorded in the DNPR.

2.1. Study design

Recurrence during follow-up was assessed using a validated algorithm, described in detail elsewhere [32]. In brief, patients who died within 180 days after surgery and patients with metastases at time of diagnosis or within 180 days after surgery were excluded as it was not relevant to investigate recurrence in these patients. Furthermore, patients with other cancers (except non-melanoma skin cancer) before the date of colorectal cancer diagnosis or within 180 days after surgery were excluded as the NPR registered metastases codes mentioned below do not distinguish between which primary cancer the metastasis was referring to. Patients were censored at time of diagnosis of a new primary tumor if it occurred after the 180 days following surgery.

In the registries described above the diagnosis of recurrence were estimated by meeting at least one of the four mentioned criteria: 1) Metastases code registered in the NPR 2) NPR-registered cytostatic therapy codes 180 or more days after the first colorectal cancer surgery and 60 or more days after the last cytostatic therapy code. 3) DPR-registered SNOMED combinations indicating recurrence. 4) An ICD-10 code specific for local colorectal cancer recurrence in the NPR any time after primary diagnosis: C18.9X and C20.9X. These codes have only been used in NPR since 2012.

The study population was followed from 180 days after surgery until death (by any cause), occurrence of a new primary tumor, end of observation (December 31, 2015), or occurrence of relapse of colorectal cancer, whichever came first.

2.2. Drug exposure and statistical methods

Diabetes was defined as medically treated diabetes, because information regarding diet-treated diabetes is not available in the registers used and because use of antidiabetics with very few exceptions indicates presence of diabetes. Study participants were classified into patients with diabetes (patients who were in active antidiabetic treatment at the beginning of the radiotherapy) and non-diabetes patients. Patients who were classified as in active treatment had to have redeemed at least one prescription for antidiabetic medication (Anatomical Therapeutic Chemical code (ATC-code), A10) in the year preceding the first date of neoadjuvant treatment and at least one redeemed prescription within 180 days after surgery. Patients with diabetes were matched with non-diabetics 1:2 by propensity score. The propensity score included age at diagnosis, sex, Charlson comorbidity index, BMI, smoking, alcohol consumption, lymph node status, and year of surgery. The matching was done by nearest neighbor matching without replacement and using a caliper of width equal to 0.2 of the standard deviation of the logit. Subgroup analysis were performed in patients receiving metformin in mono-therapy (ATC-code A10BA or A10BD) compared to non-diabetic patients.

The primary outcome of the study was disease-free survival (DFS) and the secondary outcomes were recurrence free survival (RFS) and all-cause mortality. Cox regression model was used. Disease-free survival was defined as time from 180 days after surgery to diagnosis of recurrence, new primary tumor or death regardless of cause. Recurrence-free survival was defined as time from 180 days after surgery to diagnosis of recurrence. Patients were censored at date of new primary tumor occurrence or death from any cause. All-cause mortality was defined as time from 180 days after surgery to time of death regardless of cause. Results were presented as hazard ratios (HR) with 95% confidence intervals (95% CI). The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [33] and approved by Danish Data Protection Agency (Reg- 052–2017). The statistical analysis was performed using the SAS® Proprietary Software 9.4, SAS Institute Inc., Cary, NC USA.

3. Results

A total of 9799 patients were undergoing rectal cancer surgery with curative intend in the period. Of those, 2379 received neoadjuvant treatment up to one year preceding surgery. In total 172 patients were classified as diagnosed with diabetes, of whom 58 were in monotherapy with metformin and 2056 were not using antidiabetic medication. Patients only prescribed antidiabetic medication before or after the neoadjuvant treatment were excluded (Fig. 1).

The 172 patients diagnosed with medical treated diabetes were matched by propensity score with patients not diagnosed with diabetes. It was possible to match 154 of the users to non-users, and for three patients it was only possible to match with one non-diabetes patient. The 18 patients who were not able to be matched were classified as five metformin users, eight using other antidiabetic medication and five receiving a combination of treatments and 17 of them had a Charlson Comorbidity Index > 2. In total 477 patients were included in the study; 154 with diabetes and 305 not diagnosed with medical treated diabetes, 53 in the diabetes group were treated with metformin in monotherapy. (Table 1a and Table 1b).

During follow-up, 134 patients (29.2%) were diagnosed with

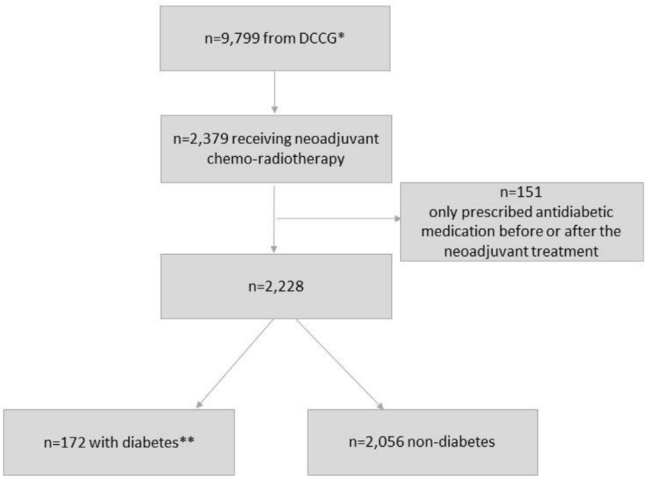

Fig. 1. STROBE flow diagram.
*Patients undergoing surgery for colorectal cancer with curative intent in the period January 1. 2003–July 1. 2015
** n = 58 metformin, n = 69 other antidiabetic medication, n = 45 treatment with a combination of the different antidiabetic medication.

recurrence 49 (31.8%) in the diabetes group and 85 (27.9%) in the non-diabetes group and 181 (39.4%) died, (59/38.3% in the diabetes group and 122/40.0% in the non-diabetes group). Concerning DFS no statistical difference between the diabetes group and the non-diabetes group was shown (HR 0.96, 95%CI 0.73–1.26, p = 0.77) and neither did the analysis regarding RFS (HR = 1.11, 95% CI 0.78–1.58, p = 0.56) nor all-cause mortality (HR = 0.94, 95% CI 0.69–1.28, p = 0.69). In the subgroup, analysis investigating metformin in monotherapy no statistical difference was shown (Table 2).

4. Discussion

The study showed no association between diabetes and response to chemo-radiotherapy in respect to DFS, RFS or all-cause mortality. Metformin use had no influence on the outcomes.

Current treatment standards for locally advanced rectal cancer involve neoadjuvant chemo-radiotherapy followed by resection. Response to the treatment is variable, and complete response leaving no residual tumor is achieved in 10–30% of the patients [34]. The factors influencing the tumor response are not well understood. Diabetes have been suggested to reduce the response to chemo-radiotherapy due to the microvascular disease limiting the drug delivery of radio sensitizing agents to the tissue as well as create a hypoxic environment that may decrease sensitivity to radiation [21]. Only a few studies have investigated this in patients with rectal cancer [21,22]. One study included 110 patients of whom only 17 had diabetes and found higher local progression rates and fewer had pathological complete response (pCR) in the diabetes group compared with the non-diabetes group [21]. Another study including only 19 patients with diabetes and 82 not diagnosed with diabetes found no difference in regard to pCR [22], which is in accordance with the findings of the present study. None of the two studies assessed DFS, RFS or all-cause mortality.

Metabolic syndrome (three of the following conditions: abdominal obesity, high fasting glucose, hypertension, hyperlipidemia or hypertriglyceridemia) and type 2 diabetes are closely related. Studies have shown that metabolic syndrome related factors such as obesity, hyperinsulinemia, hypertension and hypercholesterolemia can increase the risk of developing cancers as well as diminish response to therapies [35]. A recent study has shown that presence of risk factors for metabolic syndrome and especially hypertension is related to poorer response to chemo-radiotherapy in patients with rectal cancer [22]. In the present study, patients with diabetes are propensity score matched with non-diabetes patients taking among other things comorbidity and BMI into account. Due to the limited sample size the previous study showing a decreased response to chemo-radiotherapy in patients with diabetes were not able to adjust for possible confounders simultaneously and the factors of age, gender and BMI were examined individually. Perhaps this is the reason for the conflicting results with our study. Comorbidity plays a large role in patients with diabetes, which needs to be adjusted for when examining treatment responses in patients diagnosed with diabetes.

In multiple cancers, tumor hypoxia is a negative prognostic factor causing resistance to radiotherapy. Oxygen is consumed by proximal tumor cells causing hypoxia in tumor cells distal to blood vessels. Reducing the rate of oxygen consumption is therefore a potential strategy to reduce tumor hypoxia [23]. Metformin is thought to decrease tumor hypoxia and consequently increase response to chemo-radiotherapy. Although the mechanisms are not completely understood the major mechanism of the radio sensitizing effect is through inhibition of mitochondrial complex 1 and the mitochondrial electron transport chain and hence oxygen consumption [24,36]. A few studies have investigated the association between metformin and response to

Table 1a
Patient Characteristics at time of diagnosis.

		Diabetes	Non-diabetes
		n = 154	n = 305
Sex			
	Male	111/72.1	226/74.1
	Female	43/27.9	79/25.9
Age (years)			
	≤60	34/22.1	70/23.0
	61–70	65/42.2	115/37.7
	71–80	48/31.2	106/34.8
	> 80	7/4.6	14/4.6
Charlson Comorbidity Index			
	0	56/36.4	107/35.1
	1–2	71/46.1	156/51.2
	> 2	27/17.5	42/13.8
BMI (kg/m^2)			
	< 24.9	42/27.3	84/27.5
	25–29.9	54/35.1	98/32.1
	> 30	26/16.9	45/14.8
	Missing	32/20.8	78/25.6
Smoking			
	Current smoker	32/20.8	68/22.3
	Former smoker	57/37.0	110/36.1
	Never smoker	33/21.4	53/17.4
	Missing	32/20.8	74/24.3
Alcohol (drinks/week)**			
	0	22/14.3	43/14.1
	1–14	79/51.3	147/48.2
	15–21	10/6.5	15/4.9
	> 21	8/5.2	17/5.6
	Missing	35/22.7	83/27.2
T-stage			
	1	18/11.7	35/11.5
	2	40/26.0	68/22.3
	3	79/51.3	166/54.4
	4	11/7.1	22/7.2
	Missing	6/3.9	14/4.6
Regional lymph node metastasis			
	N0	108/70.1	211/69.2
	N1	27/17.5	58/19.0
	N2	12/7.8	23/7.5
	Nx	7/4.6	13/4.3
Year of surgery			
	2003–2007	47/30.5	100/32.8
	2008–2011	63/40.9	125/41.0
	2012–2015	44/28.6	80/26.2

Data were expressed as No./% unless otherwise indicated. Abbreviations BMI: Body Mass Index. *P-value calculated using Chi-Square test.
**Alcohol consumption 1 drink = 12 g ethanol.

Table 1b
Patient Characteristics at time of diagnosis, antidiabetic treatment.

		Metformin	Non-diabetes
		n = 53	n = 105
Sex			
	Male	41/77.4	73/69.5
	Female	12/22.6	32/30.5
Age (years)			
	≤60	13/24.5	17/16.2
	61–70	22/41.5	40/38.1
	71–80	17/32.1	41/39.1
	> 80	1/1.89	7/6.7
Charlson Comorbidity Index			
	0	25/47.2	48/45.7
	1–2	24/45.3	49/46.7
	> 2	4/7.6	8/7.6
BMI (kg/m^2)			
	< 24.9	14/26.4	26/24.8
	25–29.9	19/35.9	40/38.1
	> 30	11/20.8	12/11.4
	Missing	9/17.0	27/25.7
Smoking			
	Current smoker	14/26.4	27/25.7
	Former smoker	18/34.0	32/30.5
	Never smoker	11/20.8	22/21.0
	Missing	10/18.9	24/22.9
Alcohol (drinks/week)**			
	0	5/9.4	14/13.3
	1–14	34/64.2	53/50.5
	15–21	3/5.7	3/2.8
	> 21	2/3.8	9/8.6
	Missing	9/17.0	26/24.8
T-stage			
	1	6/11.3	10/9.5
	2	14/26.4	23/21.9
	3	27/50.9	59/56.2
	4	4/7.6	9/8.6
	Missing	2/3.8	4/3.8
Regional lymph node metastasis			
	N0	38/71.7	77/73.3
	N1	10/18.9	21/20.0
	N2	2/3.8	5/4.8
	Nx	3/5.7	2/1.9
Year of surgery			
	2003–2007	11/20.8	35/33.3
	2008–2011	21/39.6	42/40.0
	2012–2015	21/39.6	28/26.7

Data were expressed as No./% unless otherwise indicated. Abbreviations BMI: Body Mass Index. *P-value calculated using Chi-Square test.
**Alcohol consumption 1 drink = 12 g ethanol.

Table 2
Disease-free survival, Recurrence-free survival and All-cause mortality.

	n/%*	HR	95% CI	P
Disease-free survival				
Diabetes	79/51.3	0.96	0.73–1.26	0.77
Non-Diabetes	155/50.8	1		
Metformin	25/47.2	1.21	0.75–1.96	0.44
Non-Diabetes	52/49.5	1		
Recurrence-free survival				
Diabetes	49/31.8	1.11	0.78–1.58	0.56
Non-Diabetes	85/27.9	1		
Metformin	19/35.9	1.71	0.94–3.11	0.07
Non-Diabetes	25/23.8	1		
All-cause mortality				
Diabetes	59/38.3	0.94	0.69–1.28	0.69
Non-Diabetes	122/40.0	1		
Metformin	17/32.1	1.04	0.59–1.84	0.88
Non-Diabetes	41/39.1	1		

Patients with diabetes were matched with non-diabetics 1:2 by propensity score. The propensity score was estimated by age at diagnosis, sex, Charlson comorbidity index, BMI, smoking, alcohol consumption, lymph node status, and year of surgery. The patients are in the subgroup analysis classified in metformin monotherapy, other antidiabetic medication in monotherapy or in treatment with a combination of different antidiabetic medication. *the frequency and percentage of the event.

chemo-radiotherapy in patients with rectal cancer. Both studies assessed pCR as well as long-term effects such as DFS and all-cause mortality [24,25]. The studies showed conflicting results in terms of both DFS, all-cause mortality and pCR. The present study support the findings of no significant difference in terms of DFS, RFS and all-cause mortality between metformin users and non-diabetes patients. No information regarding tumor regression grade or pCR were available for this study, but even though metformin should improve tumor regression grade and pCR the impact seems not to be pronounced enough to influence DFS, RFS and all-cause mortality.

The study is a register-based observational study and has some limitations. Unmeasured confounding can be present. However, the patients were matched by propensity score based on for example comorbidity, BMI, year of surgery and thereby differences in treatments strategies are taken into account. Furthermore, only information regarding redeemed prescriptions and not actual intake was available.

As tumor regression following chemo-radiotherapy is significantly associated with all-cause mortality, DFS and local recurrence [37] an increasing interest in the understanding of treatment adjuncts to enhance tumor response to therapy is developing, and drug repurposing for anti-cancer treatments is gaining momentum. A recent review reported promising results for statins and aspirin in increasing the response to chemo-radiotherapy in patients with rectal cancer [38]. However, any new drugs given to patients already burdened by a diagnosis of cancer, radiotherapy treatment and the side effects of long course chemotherapy need to have proven efficacy. Randomized controlled trials investigating the drugs singularly or in combination to determine whether they confer an increase in response to chemo-radiotherapy are needed.

In conclusion, our study does not support that diabetes or metformin use are associated with response to neoadjuvant chemo-radiotherapy in terms of DFS, RFS or all-cause mortality.

Conflicts of interest and source of funding

The work was supported by an unrestricted grant from the Region of Zealand and the Region of Southern Denmark Joint Research Foundation. The foundation had no influence on the design or conduct of the study, collection, management, analysis or interpretation of the data or preparation, review or approval of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2018.11.007.

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