



## Metformin with neoadjuvant chemoradiation to improve pathologic response in rectal cancer: A pilot phase I/II trial

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### ABSTRACT

**Purpose:** Neoadjuvant radiotherapy with or without chemotherapy decreases the risk of local recurrence after surgery for rectal cancer. Emerging data suggest that diabetic patients on metformin may have improved cancer outcome after radiotherapy. A single institutional pilot study was performed to determine if metformin given concurrently with long course chemoradiation (CRT) may improve pathologic complete response (pCR) in non-diabetic rectal cancer patients. The study was designed to construct a confidence interval (CI) for the pCR rate to determine the sample size for a phase 2 trial.

**Methods:** Non-diabetic patients with biopsy confirmed rectal cancer deemed candidates for long course neoadjuvant CRT were invited to participate. Radiation consisted of 50.4 Gy in 28 daily fractions with concurrent daily capecitabine (825 mg/m<sup>2</sup> twice daily). Participants self-administered metformin (500 mg of twice daily) 2 weeks prior to, during and for 4 weeks after CRT.

**Results:** A total of 16 patients were accrued. One patient withdrew from the study. Only grade 1 or 2 adverse events were observed. Three patients had a clinical complete response (cCR) and did not undergo surgery. Of the 12 patients who underwent surgery, there were two pCRs. For the combined pCR/cCR rate of 33% (95% CI 19–47%), a total of 85 patients will be required to yield a 95% CI with a 10% margin of error.

**Conclusions:** Adding metformin to neoadjuvant CRT for rectal cancer does not appear to enhance toxicities. These results will be used to refine the design and conduct of a future phase 2 trial to determine whether adding metformin to CRT improves pCR/cCR rates.

### Introduction

Pre-operative or neoadjuvant radiotherapy with or without chemotherapy decreases the risk of local recurrence after surgery for rectal cancer, and is currently considered standard therapy for patients with stage II or III rectal cancer [1]. For patients with locally advanced rectal cancer, optimizing the neoadjuvant therapy may further improve locoregional control. Neoadjuvant chemoradiation (CRT) results in 15–25% pathological complete response (pCR) rates. Patients with a pCR may not benefit from definitive surgical resection [2,3]. Thus,

improving CR rates has the potential to also spare a significant number of patients from the morbidity of surgery including the need for a permanent stoma or low anterior resection syndrome.

Over the last decade, great interest has emerged in the potential use of metformin, a biguanide commonly used as first line of treatment for type 2 diabetics, in cancer treatment [4]. A growing body of epidemiologic data has demonstrated that metformin reduces cancer incidence and mortality including colorectal cancer [5–7]. In a retrospective study, diabetic rectal cancer patients on metformin was found to have improved pCR rates after neoadjuvant CRT [8]. A few recent trials

**Abbreviations:** CRT, chemoradiation; pCR, pathological complete response; CI, confidence interval; REB, Research Ethics Board; IHC-GCP, International Conference on Harmonization Good Clinical Practice; ICF, Informed Consent Form; TME, total mesorectal excision; MRI, magnetic resonance imaging; CT, computerized tomography; CBC, complete blood counts; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; cCR, clinical complete response.

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reported that metformin decreased tumor cell proliferation in non-diabetic patients [9–11]. Metformin also suppressed the number and size of pre-malignant colorectal aberrant crypt foci [12]. These clinical data have been corroborated by pre-clinical studies where metformin was shown to reduce xenograft growth after radiotherapy [13]. Prospective trials are thus warranted to assess the potential benefits of metformin in non-diabetic patients with rectal cancer.

We hypothesize that metformin improves rates of pCR in patients with rectal cancer treated with neoadjuvant CRT. The objective was to evaluate the feasibility of using metformin to improve pCR rates in non-diabetic patients undergoing standard of care neoadjuvant CRT for rectal cancer. The primary end-point was the pCR rate and its confidence interval (CI) to allow us to determine the sample size for a larger phase 2 trial.

## Materials and methods

### Study overview

This pilot phase I/II study (ClinicalTrials.gov: NCT03053544) was conducted in compliance with the trial protocol, applicable institutional Research Ethics Board (REB, #472-2015) requirements and policies, International Conference on Harmonization Good Clinical Practice (ICH-GCP) E6 guidelines and Part C Division 5 (Drugs for Clinical Trials Involving Human Subjects) of the Food and Drug Regulations as per Health Canada (No Objection Letter, metformin control number 194654). See online [supplementary file 1](#) for the protocol of the study. The REB approved Informed Consent Form (ICF) was obtained according to ICH-GCP guidelines and institutional REB policy. The complete original ICF ([supplementary file 2](#)) was maintained by the site, with a copy provided to the participant. Site monitoring was conducted by the Institutional Clinical Trials Services to ensure the safety of human study participants and compliance of study processes and documentation based on approved protocols and regulatory policies.

This study was conducted in a large tertiary cancer centre in Toronto, Ontario, Canada.

### Participants

All participants who met all of the following inclusion criteria were identified and were invited to participate in this study:

1. Male or female aged 19 or older.
2. Plan for care inclusive of:
  - i. standard of care neoadjuvant CRT
  - ii. planned total mesorectal excision (TME)
3. Histologically confirmed adenocarcinoma of the rectum.
4. Completed staging investigations including magnetic resonance imaging (MRI) of pelvis, computerized tomography (CT) of chest/abdomen/pelvis, complete blood counts (CBC), liver function test including aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and bilirubin, creatinine, carcinoembryonic antigen.
5. At least one of the following:
  - iii. T3 or T4 lesion
  - iv. T2 lesion  $\leq$  1 mm to the mesorectal fascia (low rectal cancer at or below the top border of the puborectalis with at least level 2 invasion)
  - v. Node positive rectal tumor
6. ECOG performance status of 0 or 1.

Patients with a diagnosis of diabetes, life expectancy of 6 months or less, prior pelvic radiation, serum creatinine  $> 1.5\times$ , AST or ALT  $> 2.5\times$  or bilirubin  $> 1.5\times$  upper limit of normal were ineligible. Pregnant or breastfeeding women were also excluded from participation in this study.

### Intervention

Following informed consent ([supplementary file 2](#)), participants were assigned a unique study identifier and dispensed the study drug, metformin. The intervention consisted of 3 phases.

#### Phase 1: 2 weeks prior to CRT

Participants self-administered 500 mg of metformin twice daily by mouth starting 2 weeks prior to the start of CRT. The rationale for phase 1 was to assess the feasibility of a translational component which consisted of a “research” biopsy of the tumor to assess tumor proliferation and markers of metformin activity given the known effect of metformin on tumor proliferation [9–11].

#### Phase 2: during CRT

Participants continued metformin daily throughout the course of CRT. Radiation consisted of 50.4 Gy in 28 daily fractions. All patients underwent CT simulation and radiation was delivered by volumetric intensity-modulated arc therapy with daily cone beam CT for image guidance. Capecitabine, 825 mg/m<sup>2</sup> twice daily was self-administered during the 28 days of radiation only. Participants were seen weekly during CRT including one study visit during CRT scheduled  $4 \pm 1$  week after the start of CRT. This visit included review of metformin compliance, a blood test to for CBC, creatinine, AST/ALT and bilirubin, adverse events and updates of concomitant medications.

#### Phase 3: post-CRT

Participants continued metformin at a dose of 500 mg twice daily, with the last dose at 4 weeks  $\pm$  3 days after completion of CRT. A study visit was scheduled  $7 \pm 3$  days after the stop date of metformin to coincide with the end of the adverse event reporting time period. Metformin compliance was assessed by reconciliation of unused metformin tablets and review of participant pill diaries. All participants were evaluated for adverse events from the time of their first treatment with metformin. Adverse events were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4. Surgery typically occurs at 6 to 12 weeks after end of CRT as part of standard of care at the Institution.

### Statistical and sample size considerations

All participants who received at least one week of CRT were considered completed participants and evaluable for response. The primary endpoint was the pCR rate. The definition of pCR was total regression of the primary with no tumor cells, with fibrotic tissue only with or without mucin, and lack of any evidence of lymph node metastases based on the surgical pathology report. The study was to be an internal pilot study to allow for construction of a confidence interval for the pCR rate.

The pCR rate and its associated 95% confidence intervals were estimated using unadjusted normal approximation for binomial proportions (z approximation). The null hypothesis to be tested was that the pCR rate of all evaluable participants is  $\leq 15\%$  and the alternative hypothesis is the pCR rate is greater than or equal to 25%. A pCR of  $\geq 25\%$  would justify further evaluation for a future phase 2 trial. Upon completion of the internal pilot study, the data from all participants were used to derive a formal sample size calculation for a future phase 2 trial. Since 12 participants have been shown to be the minimum number required to build a confidence interval [14], the study was designed to accrue 15 completed participants to allow for the potential of drop outs.

### Translational component

Patients were invited to participate in an optional translational study which involved a separate consent. This included a “research” biopsy by flexible sigmoidoscopy to be done after a minimum of one-week of

metformin and prior to CRT. This translational component was designed to assess tumor proliferation and hypoxia, and markers of metformin activity longitudinally using the tumor sample from the initial diagnostic biopsy, “research” biopsy taken at the start of CRT, and the final surgical specimen if applicable. Unfortunately none of the participants consented to having the optional sigmoidoscopy and biopsy. The translational component was thus not performed.

## Results

A total of 16 patients were accrued from Jan 2017–Dec 2018. One patient developed grade 2 nausea and emesis after the first dose of metformin and withdrew the consent to participate the following day. The study consisted of 14 men and one woman (age 34–81). One patient underwent emergency surgery for bowel obstruction due to an ischemic ileostomy and stopped metformin at 27 Gy. This adverse event was deemed not an adverse drug reaction and unrelated to metformin based on the Safety Monitoring Plan. He went on to complete CRT without metformin after revision of the ileostomy. This patient was considered evaluable for response as defined in the protocol. The remaining 14 patients all completed CRT as per protocol. All participants indicated that they took metformin as per protocol. One patient did not return the metformin pill bottle to the institutional pharmacy. Only 9 of 15 participants returned their metformin diaries at the end of the intervention. Table 1 outlined the clinical characteristics of the 15 patients. With the exception of the patient who developed an ischemic stoma, only grade 1 or 2 adverse events were observed (Table 2).

Three patients had a clinical complete response (cCR) and declined to have surgical resection (Table 1). All 3 remained disease free at 25, 26 and 33 months from date of informed consent on our institutional surveillance protocol. Of the 12 patients who underwent surgery (abdominoperineal resection: 2, low anterior resection: 10) 40 to 119 days (mean 84 days) after CRT, there were two pCR. Five patients had minimal residual disease, 3 had minor response, and 2 had minimal response based on the American Joint Committee on Cancer tumor regression grades. For the combined pCR/CR rate of 33% (95% CI 19–47%), a sample size of 85 patients will be needed in the phase 2 study to have a 95% CI that the CR rate is within 10% of the observed value.

## Discussion

Several randomized trials have shown that neoadjuvant radiotherapy with or without chemotherapy decreases the risks of local recurrence after surgery for rectal cancer [15–18]. Neoadjuvant

treatments do not affect survival and are associated with poorer functional outcomes such as bowel and sexual function compared with surgery alone. Recent advances in surgical techniques such as complete mesorectal resection and pre-operative MRI have suggested that MRI criteria may select patients who can be managed with surgery alone [19]. Improving the accuracy of preoperative staging is an active area of research that allows for the selection of patients who will benefit from a neoadjuvant approach. Many patients with locally advanced rectal cancer have unresectable disease or continue to develop local recurrence despite neoadjuvant CRT and aggressive resection. Optimizing the tumor response and identifying potential biomarkers represent other strategies that may lead to improved outcome. Neoadjuvant CRT results in 15–20% pCR rates. The majority of patients with a pCR may not benefit from definitive surgical resection [2,3]. Improving the pCR rates has the potential to spare a significant number of patients from the morbidity of surgery such as the need for a permanent stoma or low anterior resection syndrome.

There is extensive preclinical data to suggest that metformin has shown that metformin inhibits cancer proliferation [5,20]. Metformin is known to inhibit mitochondrial activity, leading to reduced respiration and altered redox states [21]. These biologic effects may represent the underlying mechanism of inhibition of cell proliferation by metformin [20,22]. In addition to inhibition of cancer cell proliferation, metformin might improve radiation response by decreasing tumor hypoxia-mediated radiation resistance [13]. There is preclinical evidence that metformin serves as a radiosensitizing agent and improves radiation treatment response in various cancer cell lines including colorectal cancer [13,23]. Metformin has thus been proposed as a novel radiation modifier [22,24]. In a recent retrospective study, metformin use was associated with improved tumor responses after neoadjuvant CRT in rectal cancer [25].

The optional translational study was designed with the goal to obtain a study “biopsy” to assess cancer cell proliferation and hypoxia 1 to 2 weeks after metformin and compared these biological parameters with those from the initial biopsies. Recruiting patients to participate in the translational arm of the study turned out to be challenging as none of the participants agreed to have a repeat sigmoidoscopy and biopsy outside of standard of care. Obtaining tissue samples serially for translational studies is important to better understand the putative mechanisms of experimental interventions. Strategies to enhance patients’ willingness to undergo additional sigmoidoscopy and biopsy are needed. Pertinent translational or biologic information will also need to be derived from the original biopsies or surgical specimens.

When the study was designed, the primary endpoint was pCR. Three

**Table 1**  
Clinical characteristics and pathological responses.

Patient	Distance from anal verge (cm)	Clinical stage	Size of primary (cm) <sup>1</sup>	EMVI <sup>1</sup>	EMD (mm) <sup>1</sup>	Distance to MRF (mm) <sup>1</sup>	Pathologic stage	ypT size (cm)	No. of + LNs	Radial margin (+/-)	Tumor regression grade <sup>2</sup>
1	5	T3N0	4.0	no	<1 <sup>3</sup>	10	ypT1N0	1	0/41	–	1
2	2	T3N1	3.0	yes	15	0	ypT3N0	3.5	0/6	–	2
3	7	T3N0	5.0	no	5	0	ypT2N1a	2	1/13	–	1
4	13	T3N0	6.7	yes	10	0	ypT3N0	5	0/27	+	3
5	4	T3N0	4.6	no	7	0	NA	NA	NA	–	cCR
6	8	T4aN2	4.9	yes	NA	0	ypT3N2a	2.2	6/15	–	2
7	15	T4aN1	5.0	no	NA	0	ypT4aN1b	2.5	2/25	–	1
8	13	T3N2	5.4	no	5	3	ypT0N0	0	0/20	–	0
9	8	T4bN2	7.5	yes	60	0	ypT0N0	0	0/23	–	0
10	5	T3N0	5.1	yes	4	2	ypT2N0	2.6	0/12	–	2
11	5	T3N0	2.9	no	<1 <sup>3</sup>	2	NA	NA	NA	–	cCR
12	3	T3N1	5.7	no	12	1	ypT3N2a	5.3	5/21	+	3
13	4	T3N1	4.3	yes	10	0	ypT1N1a	0.5	1/14	–	1
14	7	T3N0	3.6	no	4	28	NA	NA	NA	–	cCR
15	5.5	T3N0	6.0	no	8	8	ypT2N0	0.1	0/31	–	1

EMVI, extramural venous invasion; EMD, extramural depth; MRF, mesorectal fascia; +LNs, positive lymph nodes; +/-, positive/negative; cCR, clinical complete response; NA, not applicable; <sup>1</sup>based on MRI; <sup>2</sup>American Joint Committee on Cancer tumor regression grade: 0 = pathologic complete response, 1 = minimal residual disease, 2 = minor response, 3 = no response; <sup>3</sup>tumor speculation into perirectal fat.

**Table 2**

Adverse event grades according to Common Terminology Criteria for Adverse Events, Version 4.02.

Patient	Nausea	Vomiting	Fatigue	Hand-foot syndrome	Proctitis	Cystitis	Diarrhea	Dermatitis	Other
1	–	–	–	–	–	–	–	–	–
2	1	–	–	–	–	–	–	–	–
3	–	–	–	1	1	–	–	–	–
4	–	–	–	–	–	–	–	–	4 <sup>a</sup>
5	–	–	–	–	1	–	–	–	–
6	1	1	–	–	–	–	–	–	1 <sup>b</sup>
7	–	2	1	–	–	–	–	–	–
8	1	–	–	1	1	1	1	2	–
9	–	–	–	–	–	–	1	–	–
10	–	–	–	–	2	2	–	1	–
11	1	–	–	–	1	1	1	–	–
12	1	1	1	–	–	1	–	–	–
13	–	–	–	1	1	–	1	–	–
14	1	–	1	–	–	–	1	–	–
15	1	–	–	–	–	1	–	–	1 <sup>c</sup>

<sup>a</sup> small bowel obstruction from ischemia of ileostomy requiring surgery.<sup>b</sup> dizziness, myalgia, elevated creatinine.<sup>c</sup> myalgia.

patients elected for non-operative management demonstrated no evidence of residual or recurrent cancer at follow-up at over 2 years. It is expected that had these patients undergone TME, they would have had a pCR. In studies on neoadjuvant treatment for rectal cancer, it is expected some patients with a cCR will be reluctant to undergo surgery. Indeed, cCR patients at our institution are typically offered the option of non-operative management and close surveillance [26]. We thus reported a combined pCR/cCR rate and considered this value appropriate for future trial design.

Surprisingly of the 16 patients who consented to participate, there was only a single woman. It is unclear why this was the case. In the screening log book for participants, there was no apparent difference in the number of men or women screened or deemed eligible. In a recent analysis of the National Cancer Database, odds of achieving pCR were independently associated with female sex. Hence, the observed pCR/CR rate of 33% was unlikely skewed due to the over-representation of male patients [27].

## Conclusion

Metformin has been used for decades in patients with type 2 diabetes and has an extremely safe toxicity profile. With current interest in the use of metformin as a cancer therapeutic in non-diabetics, this study served to provide proof-of-principle data that metformin could be safely integrated into the neoadjuvant treatment of rectal cancer and to provide data to design an appropriately powered Phase 2 trial to further study this concept.

## Data availability

All data relevant to the study are included in the article. Additional data are available from the corresponding author on reasonable request.

## Ethics statement

This study was approved by the Research Ethics Board (REB) of Sunnybrook Health Sciences Centre (REB #472-2015). Prior to REB submission, the trial was reviewed and approved by the Gastrointestinal Site Group of the Odette Cancer Centre, Sunnybrook Health Sciences Centre. All participants provided signed informed consent (supplementary file 2).

## Consent for publication

All participants provided informed consent for publication of results

of the study.

## Author contributions

CSW and MK contributed to the initial design of the study. CSW, WC, SA, DF, SB contributed to recruitment of participants and data collection. AK contributed to the statistical analysis. CSW drafted the first version of the article. All authors contributed to data analysis and interpretation, revised the article and approved the final version for submission for publication. CSW had final responsibility for the decision to submit for publication. CSW had overall responsibility for the research design and implementation, including data collection, analysis and write-up.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2021.07.001>.

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