Statin therapy in patients undergoing short-course neoadjuvant radiotherapy for rectal cancer: A retrospective cohort study

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Abstract

Purpose

There is a potential benefit with concurrent statin use and neoadjuvant therapy for rectal cancer. The impact of statins on pathologic response following short-course neoadjuvant radiation has yet to be studied. This study aimed to elucidate the impact statin use on tumor response to short-course neoadjuvant radiation.

Methods

This retrospective cohort study included patients receiving short-course neoadjuvant radiation and subsequently undergoing oncologic resection for stage II/III rectal adenocarcinoma from 2014–2020. Exclusion criteria included recurrent disease, total neoadjuvant therapy (TNT), and oncologic resection less than six weeks after neoadjuvant therapy. The primary outcome was pathologic complete response (pCR). Secondary outcomes included graded pathologic response and incidence of radiation-associated toxicity. Univariable logistic regressions and stepwise multivariable logistic regressions were performed.

Results

Seventy-nine patients (mean age: 68.6 ± 11.2 years, 39.2% female) met inclusion criteria. Prior to neoadjuvant therapy, median T-stage was 3 (range: 1–4), median N-stage was 1 (range: 0–2), and mean tumor distance from the anal verge was 6.3cm (± 2.9). Thirty-five patients (44.3%) were using statins. Overall, 7.6% experienced pCR and 29.1% had no treatment response on pathology. Radiation-associated toxicity was 43.0%. Statin use was not associated with pCR (OR 2.71, 95%CI 0.47–15.7, p = 0.27), however on stepwise multivariable logistic regression, statin use was associated with decreased prevalence of no response (OR 0.08, 95%CI 0.01–0.43, p = 0.003).

Conclusions

Statins may offer a synergistic effect when given concurrently with short-course neoadjuvant radiation for rectal cancer. Further prospective study evaluating the use of statins in conjunction with neoadjuvant therapy is warranted.

Introduction

Colorectal cancer is the third most common cancer worldwide.[1] While rates are increasing, cancer specific mortality continues to decrease.[2] Advancement in surgical technique and adjunctive therapies have significantly improved both short- and long-term outcomes in these patients.[3,4] In rectal cancer patients specifically, the use of neoadjuvant protocols involving radiation alone or concurrent chemoradiotherapy has nearly halved local recurrence rates following radical oncologic resection.[5,6] Novel approaches to neoadjuvant therapy for rectal cancer include total neoadjuvant therapy (TNT) and the use of contemporary antineoplastic agents, such as bevacizumab, as chemosensitizers have demonstrated the potential to further these survival benefits.[7,8] As neoadjuvant strategies have continued to improve, attention has turned to eradication of viable tumor cells and the potential to avoid definitive oncologic resection.

Following neoadjuvant therapy, the absence of residual viable tumor cells in the surgical specimen is termed pathologic complete response (pCR).[9] This is associated with improved clinical outcomes, thus, clinicopathological predictors of pCR have become an active area of research.[10] One such potential predictor is statin use. These medications are well known for lowering low-density lipoprotein cholesterol in patients with dyslipidemia and cardiovascular disease.[11,12] More recently, statins have demonstrated benefit in oncology patients.[13,14] In colorectal cancer, statins may interfere with *Ras* oncogene activation, thus inhibiting tumor cell proliferation.[15] *Ras* oncogene activation has also been associated with reduced radio-sensitivity in rectal cancer.[16,17] Accordingly, concurrent use of statins and neoadjuvant therapy for rectal cancer has been explored.

Observational studies have demonstrated a wide range of effects from statin therapy on pCR, with some reporting statistically significant improvement.[18–20] A recent systematic review and meta-analysis demonstrated a four percent absolute increase in pCR prevalence in patients taking statins compared to patients not taking statins, which was not statistically significant.[14] Additionally, concurrent statin use may contribute to reduced treatment-related toxicity as they have demonstrated the ability to modulate acute radiotherapy-related tissue inflammatory response through inhibition of endothelial cell damage and inflammatory cytokine activation.[21,22] A phase II randomized clinical trial (RCT) is currently ongoing examining the impact of concurrent statin use and long-course neoadjuvant chemoradiation.[23] However, only one study has examined the impact of concurrent statin use in patients undergoing short-course neoadjuvant radiation.[24] Moreover, this study only reported long-term oncologic outcomes, in which they found a benefit for statin use in a subgroup of older patients. As such, the impact of statin use on short-term response to short-course neoadjuvant radiotherapy has yet to be evaluated. This is of increasing relevance as the results of the RAPIDO trial begin to disseminate into clinical practice.[25] The RAPIDO trial provides RCT evidence that short-course neoadjuvant radiotherapy in combination with a complete course of neoadjuvant systemic chemotherapy is superior to long-course neoadjuvant chemoradiotherapy in pCR and three-year disease related treatment failure. Therefore, the use of short-course neoadjuvant radiotherapy as part of neoadjuvant treatment is likely to increase.[26] Understanding the interaction between statin therapy and short-course neoadjuvant radiotherapy will be essential to inform whether incorporating statins into contemporary neoadjuvant protocols carries potential for improved outcomes. As such, this retrospective cohort study explored the impact of concurrent statin use during short-course neoadjuvant radiotherapy for rectal cancer on pathologic response.

Materials and Methods

Patient Selection

Electronic medical records (EMR) of all patients with biopsy-proven clinical stage II or III rectal adenocarcinoma undergoing short course neoadjuvant radiotherapy followed by oncologic resection at a single tertiary care centre between July 1st, 2014 and July 1st, 2020 were retrospectively searched. Patients were included if their EMR contained a pathologist report of pathologic tumor stage according to the American Joint Committee on Cancer (AJCC) staging system for colorectal cancer and a tumor regression grade.[27,28] Patients were excluded if they underwent long-course neoadjuvant chemoradiotherapy, immunotherapy, total neoadjuvant therapy, or if they failed to complete 80% or more of their planned neoadjuvant radiation. Patients with recurrent rectal cancer were excluded. Patients undergoing definitive oncologic resection less than six weeks following the receipt of their last dose of neoadjuvant radiation were excluded. This retrospective cohort study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[29] Local ethics review board approval was obtained prior to commencement of the study.

Treatment Details

All patients were evaluated by a surgeon, a medical oncologist, and a radiation oncologist following completion of their staging investigations which consisted of a carcinoembryonic antigen (CEA), computed tomography (CT) of the chest, abdomen, and pelvis with intravenous contrast, and magnetic resonance imaging (MRI) of the pelvis with gadolinium. All included patients underwent locoregional short-course neoadjuvant radiotherapy, receiving 25-gray (Gy) in five daily fractions to a clinical target volume consisting of the rectal primary and the mesorectal, presacral, internal iliac, and lower common iliac lymph node regions. Treatment was planned and administered using either intensity-modulated radiation therapy or volumetric modulated arc therapy. “Watch-and-wait” protocols were not available at our institution during the study period and thus all included patients proceeded to oncologic resection between 6- and 12-weeks following completion of their neoadjuvant radiation. Patients underwent tumor-specific total mesorectal excision.[30] Resections were performed either via laparotomy or laparoscopy, based on patient- and tumor-factors, as well as surgeon preference. All resected surgical specimens underwent sectioning and pathologic tumor staging according to Quirke's methodology.[31,32] Pathology synoptic reports were standardized according to Cancer Care Ontario.[33]

Outcomes Assessed

The primary outcome was pCR. The definition of pCR for the purposes of the present study was the absence of residual viable tumor cells within the area of rectum treated with neoadjuvant radiotherapy on postoperative pathological evaluation of a surgical specimen derived from an oncologic resection.[27]

The secondary outcomes included graded pathologic response, prevalence of radiation-associated toxicity, and MRI-based tumor regression grade (mrTRG). The graded pathologic response was according to the AJCC criteria for determining pathologic response to neoadjuvant radiotherapy for rectal cancer proposed by Mace *et al.*[34] The grading system was adopted as follows: TRG 0 = no viable tumor cells detected (pCR); TRG 1 = a single or a small group of malignant cells observed (good response); TRG 2 = residual malignant cells that have been outgrown by fibrosis (some response); TRG 3 = minimal or no destruction of previously identified malignant cells (no response).[34] Radiation-associated toxicity was evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[35] The mrTRG is a five-point scale used to classify the degree of tumor regression from pre-neoadjuvant MRI to post-neoadjuvant MRI T2-weighted images and correlates with pCR.[36,37]

Data Collection

Three study personnel extracted data onto a data collection manual designed *a priori*. Baseline patient characteristics as well as preoperative MRI reports, neoadjuvant therapy information, surgical pathology reports, and medical oncology, radiation oncology, and surgical follow up dictations were accessed through institution specific EMRs. Standardized Cancer Care Ontario synoptic pathology reports were reviewed for details pertaining to neoadjuvant treatment response and pathologic cancer staging. Adverse reactions secondary to radiotherapy were found in dictated radiation and surgical follow-up documentation. The mrTRGs were abstracted from post-neoadjuvant MRI reports.

Statistical Analysis

Descriptive statistics were used to characterize the sample population. Continuous variables were described as means with standard deviations, while categorical variables were reported as proportions. Statistical significance was set at $p < 0.05$ *a priori* and 95% confidence intervals were provided where applicable. Independent two-tailed t-

tests, Mann-Whitney U tests, and the Chi-Square test were performed to determine differences in patient, disease, and treatment characteristics, as well as treatment response between statin users and non-users for normally distributed continuous variables, non-normally distributed continuous variables, and categorical variables, respectively. Univariable logistic regression analyses were performed to estimate the association of patient, tumor, and treatment characteristics with the primary and secondary outcomes. A stepwise multivariable logistic regression model was then fitted for outcome variables with at least one significant association demonstrated on univariable logistic regression. Data were analyzed using STATA (StataCorp, version 15; College Station, TX).

Results

Patient Characteristics

Following review of 182 patient charts, 79 patients (39.2% female, mean age: 68.6 ± 11.2 years) met inclusion criteria. The chart review process is highlighted in the STROBE flow diagram in Fig. 1. There were 35 patients (44.3%) using statins at the commencement of their neoadjuvant therapy. All patients but one received 25.0-Gy of pelvic radiation dosed in five fractions over the course of five to seven days. The patients in the statin group were significantly older (statin: 71.9 ± 10.7 years, no statin: 65.9 ± 11.0 years, $p = 0.02$). There was no significant difference in Charlson Comorbidity Index (CCI) between groups (statin: 6.0 ± 2.0, no statin: 5.2 ± 1.9, $p = 0.07$). Significantly more patients in the statin group were prescribed metformin (statin: 28.6%, no statin: 9.1%, $p = 0.02$) and aspirin (statin: 37.1%, no statin: 2.3%, $p < 0.001$). Further patient characteristics are in Table 1.

Disease Characteristics

The median pre-neoadjuvant clinical T- and N-stages were III (range: I-IV) and I (range: 0-II), respectively. The median post-neoadjuvant clinical T- and N-stages were II (range: 0-IV) and 0 (range: 0–2), respectively. The median pathologic T- and N-stages were III (range: 0-IV) and 0 (range: 0-II), respectively. The distribution of pathologic stages was as follows: 27.8% stage I, 27.9% stage II, and 36.7% stage III. There were no significant differences in clinical stage between statin users and non-users (Table 1).

Tumor Response

Six patients experienced pCR (7.6%). There was no significant difference in prevalence of pCR between statin users and non-users (statin: 11.4%, no statin: 4.5%, $p = 0.25$). Evaluation of graded pathologic responses demonstrated that fewer statin users experienced TRG 3 (i.e., no response) as compared to non-users (statin: 17.1%, no statin: 38.6%, $p = 0.04$). There was no significant difference in statin users and non-users in the number of observed “good response” grades (statin: 20.0%, no statin: 13.6%, $p = 0.45$) and “some response” grades (statin: 51.4%, no statin: 43.2, $p = 0.47$). Only 11 of the included patients had mrTRG reported on their post-neoadjuvant therapy MRI and there was no significant difference between groups (Table 1).

The associations between graded pathologic response and patient, treatment, and pre-neoadjuvant disease characteristics are presented in Table 2. There was no significant association observed with any of the included variables.

On univariable logistic regression analysis of the prevalence of pCR with patient, treatment, and pre-neoadjuvant disease variables, there were no significant associations observed (Table 3). Similarly, there were no variables significantly associated with good pathologic response or some pathologic response. Univariable logistic regression analysis of the prevalence of TRG 3 (i.e., no response) to neoadjuvant therapy with patient, treatment, and pre-

neoadjuvant disease variables, statin use was the only statistically significant association (OR 0.33, 95%CI 0.11–0.96, p = 0.04). A subsequent stepwise multivariable logistic regression analysis found statin use (OR 0.08, 95%CI 0.01–0.43, p = 0.003) and pre-neoadjuvant clinical N-stage (OR 0.37, 95%CI 0.14–0.99, p = 0.05) to be associated with a significant decrease in prevalence of TRG 3 (i.e., no response) to neoadjuvant therapy (Table 4).

Given the lack of reporting with regards to mrTRG, a logistic regression analysis was not performed for this outcome.

Adverse Events

Overall, 34 (43.0%) patients experienced an adverse event secondary to neoadjuvant therapy (Table 1). The majority of adverse events were CTCAE Grade I (67.6%). Five patients (6.5%) had adverse events of Grade III or higher; none of these patients were statin users. There was no significant difference between statin users and non-users in prevalence of neoadjuvant therapy-associated adverse events (statin: 37.1%, no statin: 47.7%, p = 0.34). No patient, disease, or treatment characteristics were significantly associated with the development of neoadjuvant treatment related adverse events on univariable logistic regression.

Discussion

The present retrospective cohort study examined statin use as a clinical predictor of pCR using a retrospective cohort of 79 patients undergoing short-course neoadjuvant radiotherapy followed by oncologic resection. While there was no association demonstrated between statin use and pCR, a statistically significant inverse relationship was observed between statin use and no pathologic evidence of neoadjuvant treatment response on multivariable stepwise logistic regression (OR 0.08, 95%CI 0.01–0.43, p = 0.003). There were no other clinicopathologic predictors of pCR identified. There was no observed association between statin use and neoadjuvant therapy-associated adverse events, nor was there a significant difference between statin users and non-users in terms of prevalence of adverse events (p = 0.34).

All included patients in the present study underwent short-course neoadjuvant radiotherapy, which included five fractions over the course of five-to-seven days with 5.0-Gy delivered each treatment for a total of 25.0-Gy. Historically, short-course neoadjuvant radiotherapy was followed by immediate surgery (i.e., within 1–2 weeks), which resulted in less pathologic tumor response as compared to long-course neoadjuvant chemoradiotherapy which was traditionally followed by delayed surgery.[40] However, in the present study, patients underwent definitive oncologic resection between 6- and 12-weeks following completion of short-course neoadjuvant therapy. The Stockholm III trial demonstrated improved pCR and lower surgical morbidity in patients undergoing neoadjuvant radiation protocols that involved delayed oncologic resection (i.e., 4–8 weeks following completion of neoadjuvant therapy). As such, neoadjuvant therapy with delayed surgery is recommended as standard of care in the most recent National Comprehensive Cancer Network (NCCN) guidelines for rectal cancer.[43]

More recently, TNT protocols with short-course radiotherapy have been applied to the management of locally advanced rectal cancer. The RAPIDO trial is a multi-center, phase III RCT published in 2021 that compared short-course radiotherapy followed by full-dose chemotherapy (i.e., six cycles of CAPOX or nine cycles of FOLFOX4) to long-course chemoradiotherapy followed by delayed surgery and optional adjuvant chemotherapy in patients with locally advanced rectal cancer.[25] The TNT group experienced significantly less disease-related treatment failure compared to the standard long-course chemoradiotherapy group (HR 0.75, 95%CI 0.60–0.95, p = 0.019). Twice as many patients in the TNT group experienced pCR (28% vs. 14%, p < 0.0001). Similarly, in the more recently published STELLAR trial, which compared short-course radiotherapy plus four-cycles of CAPOX to long-course neoadjuvant

chemoradiotherapy, pCR prevalence was significantly greater in the TNT group (21.8% vs. 12.3%, p = 0.002).[44] This trial also demonstrated significantly improved three-year OS with the use of TNT (HR 0.67, 95%CI 0.46–0.97, p = 0.03). Evidence is also building for TNT protocols involving long-course chemoradiotherapy.[38,39] Altogether, TNT protocols are increasingly relevant for managing locally advanced rectal cancer, some of which incorporate short-course radiotherapy.[26] Secondary analyses of the above RCTs to determine if there is an association between statin use and pathologic or clinical response could be an important initial step in evaluating the impact of statins on these novel protocols.

While TNT protocols offer significant promise with regards to pathologic tumor response, there are potential downsides with regards to treatment-related adverse events. In the STELLAR trial, the risk of CTCAE Grade 3–5 toxicity in the TNT arm was double that of the long-course neoadjuvant chemoradiotherapy arm (26.5% vs. 12.6%, p < 0.001).[44] Unsurprisingly, the same trial demonstrated a significant reduction in percentage of completed treatments in the TNT group.[44] As such, the importance of interventions aimed at reducing treatment toxicity is furthered by the advent of TNT. Preclinical studies suggest statins may inhibit radiation-induced fibrosis and enteropathy through inhibition of the *Rho* pathway.[21,22] Human studies offer less conclusive findings regarding the association between statin use and reduced radiation-induced toxicity.[19,45] Mace *et al.* conducted a prospective cohort study comparing statin users and non-users receiving long-course neoadjuvant therapy for rectal cancer and demonstrated a radiation-induced toxicity incidence of 2.0% over twelve years.[45] Only one of these patients experiencing an adverse event was on a statin at the time. The overall event rate was too low to adequately assess for a statistically significant association. In the present study, there was a 10% absolute decrease in prevalence of radiation induced toxicity according to the CTCAE classification, which did not reach statistical significance. Nonetheless, statins are safe medications with a very low prevalence of associated adverse events, and concurrent use with neoadjuvant therapy for rectal cancer does not appear to worsen neoadjuvant therapy-associated toxicity.[46]

The strengths of the present study include methodological rigour, a thorough chart review, and novelty. This is the first study examining the association between statin use and pathologic tumor response in patients receiving short-course neoadjuvant radiotherapy. This study also has several limitations. First, there were only 79 patients who met inclusion criteria. The event rate for pCR was six (7.6%); thus, the study was underpowered for detecting any significant association between clinicopathologic variables and pCR.[14] Second, this was a retrospective study and therefore has the inherent risk of residual confounding and selection bias. For example, we did not explore time to surgery as a predictor variable associated with pCR. It is possible that differences in response between a 6-week delay and a 12-week delay to surgery are a source of residual confounding in the present study. The data abstraction performed as part of this retrospective chart review was thorough and captured several possible confounders and effect modifiers that allowed for a multivariable analysis in attempt to control for some of the confounding present in this study. Moreover, consecutive sampling was used to reduce selection bias. Third, there were important baseline differences between groups, such as age, metformin use, and aspirin use. Metformin use and aspirin use have both been associated with increased pathologic downstaging of rectal tumors following neoadjuvant treatment.[49] In the present study, neither were associated with graded pathologic response on logistic regression. Fourth, only 11 of the included patients had mrTRG reported on post-neoadjuvant pelvic MRI, thus we were unable to adequately analyze the association between statin use and radiographic response to neoadjuvant therapy. Last, patients undergoing TNT and patients enrolled in watch-and-wait protocols were excluded. While we analyzed a homogeneous patient population, the findings are less generalizable to patients enrolled in these more contemporary protocols that are likely to become increasingly relevant.

Statin use is a modifiable variable that, while not positively associated with pCR in the present study, did demonstrate promise in reducing the prevalence of a poor pathologic response to short-course neoadjuvant radiotherapy for rectal cancer, which may be associated with survival outcomes. Overall, its use in patients with rectal cancer may offer a safe, synergistic effect when given concurrently with short-course neoadjuvant radiation. Further prospective study evaluating the use of statins in conjunction with contemporary TNT approaches to locally advanced rectal cancer is warranted.

Declarations

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Contributions:

Study concept and design – All authors

Acquisition of data – McKechnie, Schep, Cardenas

Analysis and interpretation of data – All authors

Drafting and revision of manuscript – All authors

Approval of the final version of the manuscript – All authors

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Tables

Table 1 – Patient characteristics, disease characteristics, and neoadjuvant treatment response according to statin use (N, number of patients; SD, standard deviation; BMI, body mass index; CCI, Charlson Comorbidity Index; ASA, aspirin; T stage, tumor stage; N stage, nodal stage; cm, centimeters; CRM, circumferential resection margin; pCR, pathological complete response; mrTRG, magnetic resonance tumor regression grade; CTCAE, Common Terminology Criteria for Adverse Events)

Characteristic	Overall	Statin	No Statin	*P*
	N=79	*N=35*	*N=44*	
Demographics				
Age, years (mean [SD])	68.6 (11.2)	71.9 (10.7)	65.9 (11.0)	0.02
Female (N [%])	31 (39.2)	15 (42.9)	16 (36.4)	0.56
BMI (mean [SD])	29.6 (7.7)	30.6 (9.2)	28.8 (6.4)	0.40
Smoker (N [%])	27 (34.6)	14 (40.0)	13 (30.2)	0.37
CCI (mean [SD])	5.5 (2.0)	6.0 (2.0)	5.2 (1.9)	0.07
Other medications				
Metformin (N [%])	14 (17.7)	10 (28.6)	4 (9.1)	0.02
ASA (N [%])	14 (17.7)	13 (37.1)	1 (2.3)	<0.001
Immunosuppressants (N [%])	2 (2.5)	2 (5.7)	0	0.11
Neoadjuvant Radiation Treatment				
Fractions (mean [SD])	5 (0)	5 (0)	5 (0)	-
Gray (mean [SD])	25.0 (0.23)	25.0 (0)	24.9 (0.30)	0.38
Pre-Neoadjuvant Disease				
T stage (median [range])	3 (1-4)	3 (1-4)	3 (2-4)	0.20
N stage (median [range])	1 (0-2)	1 (0-2)	1 (0-2)	0.19
Threatened CRM (N [%])	24/71 (33.8)	10/33 (30.3)	14/38 (36.8)	0.56
Cm from anal verge (mean [SD])	6.3 (2.9)	6.2 (2.9)	6.4 (3.0)	0.76
Craniocaudal extent (mean [SD])	4.8 (1.8)	4.9 (1.9)	4.7 (1.7)	0.77
Post-Neoadjuvant Disease *(N=18)*				
T stage (median [range])	2 (0-4)	2 (2-3)	2 (0-4)	0.63
N stage (median [range])	0 (0-2)	0 (0-1)	0 (0-2)	0.55
Threatened CRM (N [%])	2/16 (12.5)	1/6 (16.7)	1/10 (10.0)	0.70
Cm from anal verge (mean [SD])	6.4 (3.1)	5.8 (3.7)	6.9 (2.7)	0.49
Craniocaudal extent (mean [SD])	3.6 (1.5)	3.7 (0.95)	3.5 (1.93)	0.85
Pathological Disease Staging				
T stage (median [range])	3 (0-4)	2 (0-3)	3 (0-4)	0.26
N Stage (median [range])	0 (0-2)	0 (0-2)	0 (0-2)	0.55
Stage I (N [%])	22 (27.8)	11 (31.4)	11 (25.0)	0.53
Stage II (N [%])	22 (27.9)	9 (25.7)	13 (29.5)	0.70

Stage III (N [%])	29 (36.7)	11 (31.4)	18 (40.9)	0.17
Grade (median [range])*	1 (0-3)	1 (0-3)	1 (0-3)	0.21
Neoadjuvant Treatment Response				
No response (N [%])	23 (29.1)	6 (17.1)	17 (38.6)	0.04
Some response (N [%])	37 (46.8)	18 (51.4)	19 (43.2)	0.47
Good response (N [%])	13 (16.5)	7 (20.0)	6 (13.6)	0.45
pCR (N [%])	6 (7.6)	4 (11.4)	2 (4.5)	0.25
mrTRG (median [range])	2 (0-4)	2 (1-4)	2 (0-3)	0.26
Adverse Neoadjuvant Response				
CTCAE Grade 1 (N [%])	23 (29.1)	11 (31.4)	12 (27.3)	0.69
CTCAE Grade 2 (N [%])	6 (7.6)	2 (5.7)	4 (9.1)	0.57
CTCAE Grade 3 (N [%])	4 (5.1)	0	4 (9.1)	0.07
CTCAE Grade 4 (N [%])	1 (1.3)	0	1 (2.3)	0.37
CTCAE Grade 5 (N [%])	0	0	0	-

*Grade 1 = well differentiated, Grade 2 = moderately differentiated, Grade 3 = poorly differentiated

Table 2 – Association between patient characteristics, treatment characteristics, and pre-neoadjuvant disease characteristics and graded pathologic response to neoadjuvant therapy (N, number of patients; SD, standard deviation; mins, minutes; BMI, body mass index; pCR, pathologic complete response; CCI, Charlson Comorbidity Index; ASA, aspirin; T stage, tumor stage; N stage, node stage; CRM, circumferential resection margin; Cm, centimeters)

	Pathologic Response				Total	P-Value
	No response	Poor response	Good response	pCR		
	N = 23	*N = 37*	*N = 13*	*N = 6*	*N = 79*	
Patient Characteristics*						
Female	11 (47.8)	11 (29.7)	7 (53.9)	2 (33.3)	31 (39.2)	0.34
Age (SD)	67.2 (11.5)	68.0 (8.8)	72.8 (15.1)	67.8 (14.0)	68.6 (11.2)	0.09
BMI (SD)	32.1 (10.1)	28.3 (6.5)	29.5 (8.4)	28.9 (3.4)	29.6 (7.8)	0.07
Smoker	9 (39.1)	11 (30.6)	4 (30.8)	3 (50.0)	27 (34.6)	0.76
CCI (SD)	5.3 (2.2)	5.3 (1.6)	6.5 (2.3)	5.8 (2.5)	5.5 (2.0)	0.17
Treatment Characteristics*						
Statin	6 (26.1)	18 (48.7)	7 (53.9)	4 (66.7)	35 (44.3)	0.17
ASA	4 (17.4)	8 (21.6)	1 (7.7)	1 (16.7)	14 (17.7)	0.73
Metformin	5 (21.7)	5 (13.5)	2 (15.4)	2 (33.3)	14 (17.7)	0.63
Pre-Neoadjuvant Disease Characteristics*						
T stage (range)	3 (1-4)	3 (2-4)	3 (2-4)	3 (2-3)	3 (1-4)	0.52
N stage (range)	0 (0-2)	1 (0-2)	1 (0-2)	0.5 (0-2)	1 (0-2)	0.90
Extra-mesorectal nodes	3 (14.3)	6 (17.7)	1 (9.1)	1 (25.0)	11/70 (15.7)	0.86
Threatened CRM	5 (23.8)	12 (34.3)	5 (45.5)	2 (50.0)	24/71 (33.8)	0.56
Cm from anal verge (SD)	5.9 (2.6)	6.2 (2.9)	6.8 (3.3)	8.5 (3.0)	6.3 (2.9)	0.84
Craniocaudal extent (SD)	4.7 (1.8)	4.9 (1.8)	5.1 (1.8)	4.2 (2.1)	4.8 (1.8)	0.97
% Circumference	0.66 (0.27)	0.78 (0.26)	0.57 (0.33)	0.65 (0.37)	0.70 (0.29)	0.64

* Values represent n (%) unless otherwise specified

Table 3 – Univariable logistic regression analyses of patient demographic, treatment, and MRI characteristics with pCR and no response (pCR, pathologic complete response; OR, odds ratio; CI, confidence interval; y, years; kg, kilograms; m, meters; BMI, body mass index; CCI, Charlson Comorbidity Index; MRI, magnetic response imaging; T stage, tumor stage; N stage, node stage; CRM, circumferential resection margin; Cm, centimeters)

	pCR			No response		
	OR	95% CIs	*P*-Value	OR	95% CIs	*P*-Value
Patient Variables						
Age (y)	0.99	0.92-1.07	0.87	0.98	0.94-1.03	0.49
Female	0.76	0.13-4.41	0.76	1.65	0.62-4.41	0.32
BMI (kg/m^2)	0.99	0.87-1.12	0.82	1.06	0.98-1.14	0.15
Smoker	2.00	0.38-10.66	0.42	1.32	0.48-3.63	0.59
CCI	1.08	0.71-1.64	0.71	0.90	0.70-1.16	0.42
Treatment Variables						
Statin	2.71	0.47-15.7	0.27	0.33	0.11-0.96	0.04
Aspirin	0.92	0.10-8.58	0.94	0.97	0.27-3.47	0.96
Metformin	2.54	0.42-15.48	0.31	1.45	0.43-4.92	0.55
Pre-Neoadjuvant MRI Variables						
T stage	0.65	0.17-2.43	0.52	0.89	0.40-1.98	0.77
N stage	1.02	0.36-2.91	0.97	0.75	0.40-1.40	0.36
Extra-mesorectal nodes	1.87	0.18-19.79	0.60	0.85	0.20-3.60	0.83
Threatened CRM	2.04	0.27-15.50	0.49	0.51	0.16-1.62	0.25
Cm from anal verge	1.28	0.92-1.78	0.14	0.93	0.77-1.12	0.44
Craniocaudal extent (cm)	0.80	0.46-1.41	0.45	0.95	0.71-1.27	0.73
% Circumference	0.55	0.03-9.71	0.68	0.54	0.09-3.27	0.50

Table 4 – Stepwise logistic regression multivariable analyses of the association of patient demographic, treatment, and MRI characteristics with no response (OR, odds ratio; CI, confidence interval; pCR, pathologic complete response; CCI, Charlson Comorbidity Index; N stage, node stage; CRM, circumferential resection margin)

Characteristic	No Response		
	OR	95% CIs	*P*-Value
Age (y)	0.93	0.84-1.03	0.17
Female	3.69	0.88-15.50	0.08
CCI	1.54	0.83-2.87	0.17
Statin	0.08	0.01-0.43	0.003
Metformin	6.65	0.92-48.12	0.06
Pre-Neoadjuvant N Stage	0.37	0.14-0.99	0.05
Pre-Neoadjuvant Threatened CRM	0.26	0.05-1.29	0.10
Pre-Neoadjuvant % Circumference	0.30	0.03-3.18	0.32

Figures

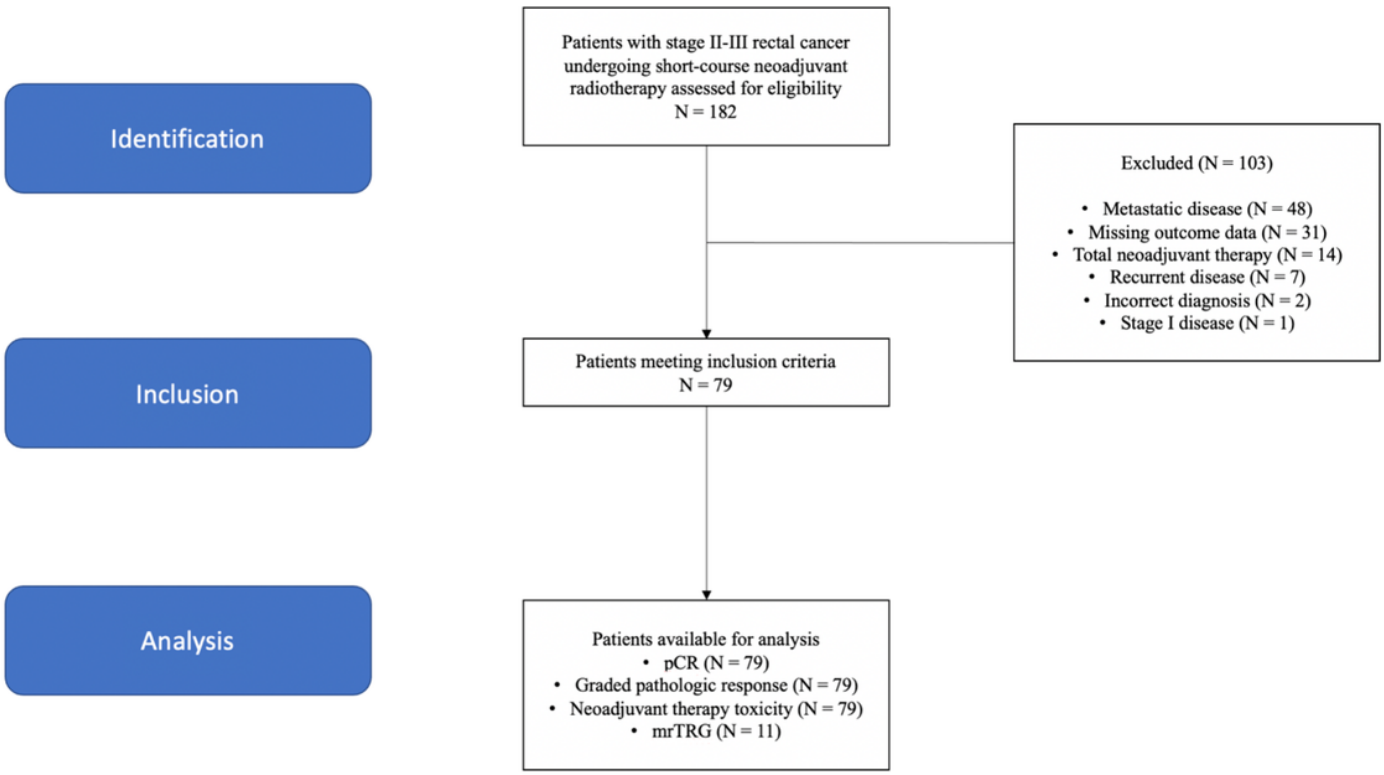

Figure 1

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow diagram.

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