



Outcome of Patients Treated with Neoadjuvant Concurrent Chemoradiation for Signet Ring Cell Rectal Carcinoma

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ABSTRACT

Background: Signet-ring cell carcinoma (SRCC) of the rectum is a rare and aggressive subtype of colorectal cancer, often presenting at a younger age and with advanced disease. It has historically shown limited response to standard neoadjuvant chemoradiotherapy (CRT), with poor long-term outcomes. This study aimed to evaluate short-term clinical and pathological outcomes following neoadjuvant concurrent CRT in patients with rectal SRCC. **Methods:** This descriptive case series included 30 patients with histologically confirmed rectal SRCC treated between December 2023 and December 2024. All received induction CapeOX chemotherapy followed by CRT and total mesorectal excision (TME). Radiological response was assessed using RECIST 1.1 criteria and MRI. Primary outcomes included pathological complete response (pCR) and downstaging; secondary outcomes included R0 resection rates and treatment-related toxicities. **Results:** The median age was 42 years; 60% of patients presented with stage III disease. Of 29 patients who completed CRT, 26 underwent surgery. Pathological complete response was achieved in 15.4%, and 57.7% had overall downstaging. R0 resection was accomplished in 88.5%. Radiologically, 27.6% had partial response, 62.1% had stable disease, and no complete radiological responses were observed. Treatment-related grade 3 toxicities occurred in 40% of patients. No treatment-related mortality was reported. **Conclusion:** Neoadjuvant concurrent CRT in rectal SRCC resulted in modest tumor regression and a pCR rate consistent with previous literature. However, the majority of patients proceeded to successful resection with acceptable toxicity. These findings support the feasibility of an intensified neoadjuvant approach in this histologically aggressive subtype, although long-term survival benefits remain to be established.

INTRODUCTION

Signet-ring cell carcinoma (SRCC) of the rectum is an uncommon histological subtype of colorectal adenocarcinoma, representing approximately 1% of cases, although reported incidences range from 1% to 13% across different series [1,2]. It is defined by the presence of more than 50% tumor cells containing intracytoplasmic mucin that displaces the nucleus peripherally, giving rise to the characteristic "signet-ring" morphology [2,3]. Patients with rectal SRCC tend to present at a younger age and often at advanced stages, with transmural extension, nodal involvement, or peritoneal spread already evident at diagnosis [4,5].

The prognosis of rectal SRCC is markedly worse than that of conventional adenocarcinoma. Multiple large-scale studies have confirmed signet-ring histology as an independent adverse prognostic factor, associated with increased risk of recurrence and mortality even after stage

adjustment [6,7]. Reported 5-year survival rates are frequently below 30%, and outcomes remain poor despite multimodal management [2,3]. The aggressive clinical behavior of SRCC is thought to arise from its infiltrative growth pattern, early peritoneal dissemination, and poor differentiation, which together contribute to low curative resection rates and a high likelihood of early relapse [6,8]. For locally advanced rectal cancer, the standard treatment paradigm consists of neoadjuvant concurrent chemoradiotherapy (CRT) followed by total mesorectal excision (TME) and adjuvant systemic therapy [9]. In general rectal cancer populations, preoperative CRT has been shown to improve local control, enhance resectability, and increase the likelihood of sphincter preservation, with pathological complete response (pCR) serving as a surrogate marker for long-term survival [4]. However, mounting evidence indicates that SRCC responds poorly to conventional CRT, with substantially

lower tumor regression rates, reduced pCR rates, and inferior survival outcomes compared with non-SRCC adenocarcinoma [1,10,11]. In one institutional series, only 56% of patients achieved sufficient downstaging to undergo surgical resection, and among those resected, early recurrence occurred in the majority [1]. Recent propensity-matched analyses confirm consistently poorer survival for SRCC, with 5-year overall survival rates of 34% compared with more than 70% for conventional adenocarcinoma [3].

Despite occasional reports of comparable tumor regression after CRT, these findings have not translated into durable improvements in survival [3,12]. Intensified treatment strategies such as total neoadjuvant therapy (TNT) have been explored, showing potential improvements in compliance and pathological response in broader rectal cancer cohorts, but survival benefits specific to SRCC remain unproven [13,14]. Emerging approaches, including molecularly guided therapy and immunotherapy, are under early investigation but are not yet standard of care [15,16].

Given its rarity, most available data on rectal SRCC come from retrospective analyses or small case series, leaving important gaps in evidence regarding optimal management. This study was therefore undertaken to evaluate short-term outcomes in patients with rectal SRCC treated with neoadjuvant concurrent chemoradiotherapy, focusing on radiological and pathological response, resectability, and early oncologic outcomes.

MATERIALS AND METHODS

This descriptive case series was carried out at Shaikat Khanum Memorial Cancer Hospital and Research Centre between December 2023 and December 2024. The study protocol was approved by the Institutional Review Board and Ethics Committee, and all patients provided written informed consent in accordance with the Declaration of Helsinki.

Sample size estimation was based on previous reports indicating pathological complete response rates between 10% and 23% in signet-ring cell carcinoma patients treated with neoadjuvant chemoradiotherapy. Using a 95% confidence interval and a 10% margin of error, the minimum required sample size was calculated to be 25. To accommodate possible loss to follow-up and incomplete data, the final target was set at 30 patients.

Patients were eligible if they had histologically confirmed rectal adenocarcinoma with $\geq 50\%$ signet-ring cells, tumor located within 15 cm of the anal verge, and stage II or III disease based on MRI and CT staging. Additional requirements included age ≥ 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate bone marrow, hepatic, and renal function. Patients with previous pelvic radiotherapy, prior chemotherapy for rectal cancer, distant metastasis at diagnosis, or comorbidities precluding safe treatment were excluded. Pregnancy, inflammatory bowel disease, and inability to comply with treatment or follow-up were also exclusion criteria.

Baseline data collection included demographics, performance status, clinical presentation, and tumor characteristics. Staging was performed with pelvic MRI

and CT chest–abdomen–pelvis. Laboratory investigations such as complete blood counts, liver and renal function tests, and carcinoembryonic antigen (CEA) were obtained at enrollment. Histopathological review confirmed tumor grade, the percentage of signet-ring cells, and the presence of lymphovascular or perineural invasion.

All patients received induction chemotherapy with CapeOX (capecitabine and oxaliplatin) administered every 21 days for six cycles. After completion of induction therapy, a 3-week interval was observed before commencing concurrent chemoradiotherapy. During chemoradiation, patients received oral capecitabine at a dose of 825 mg/m² twice daily on weekdays only, serving as a radiosensitizer. Radiotherapy was delivered using either intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) following CT simulation with appropriate bladder and bowel preparation. A pelvic dose of 45 Gy in 25 fractions was prescribed, with a simultaneous integrated boost (SIB) to 50 Gy in 25 fractions directed at the gross tumor volume. Treatment fields encompassed the tumor, mesorectum, presacral space, and internal iliac nodal basins, with margins applied as per institutional standards. Treatment was delivered once daily, five days a week, over approximately five weeks.

Response assessment was performed at week 7 following completion of chemoradiotherapy, with radiological evaluation using CT chest–abdomen–pelvis (CT CAP) and pelvic MRI. At week 8, all patients proceeded to surgery in the form of total mesorectal excision (TME). The surgical approach was individualized, with low anterior resection (LAR) or abdominoperineal resection (APR) performed depending on tumor location, sphincter involvement, and resectability. The objective of surgery was complete (R0) resection with negative margins. All resected specimens underwent standardized pathological examination, including assessment of tumor regression grade, circumferential resection margin, and lymph node status. The primary outcomes of the study were radiological response assessed on CT CAP and MRI, and pathological response determined on resected specimens, including the rate of pathological complete response (ypT0N0). Secondary measures included resectability, R0 resection rates, and treatment-related toxicities graded according to CTCAE version 5.0.

Patients were reviewed weekly during chemoradiotherapy for clinical monitoring and toxicity assessment. After surgery, follow-up was scheduled at three-month intervals during the first year, with clinical evaluation, laboratory studies, and imaging where indicated. Statistical analysis was conducted using SPSS version 28.0 (IBM Corp, Armonk, NY). Continuous variables were presented as mean \pm standard deviation or median with interquartile range, while categorical variables were reported as frequencies and percentages. Group comparisons were made using Student's t-test or Chi-square test where appropriate, with statistical significance set at $p < 0.05$.

RESULTS

The median age was 42 years (range 28–67 years), with a predominance of male patients (18 patients, 60%). The

majority of patients presented with a good performance status, with 23 patients (76.7%) having an Eastern Cooperative Oncology Group performance status of 0, and 7 patients (23.3%) having a status of 1.

Clinical staging at presentation revealed that 12 patients (40%) had stage II disease, while 18 patients (60%) presented with stage III disease. The median distance from the anal verge was 8.5 cm (range 4-14 cm). Baseline carcinoembryonic antigen levels were elevated (>5 ng/mL) in 19 patients (63.3%), with a median value of 12.4 ng/mL (range 2.1-84.6 ng/mL). Histopathological analysis confirmed that all patients had greater than 50% signet-ring cells, with 22 patients (73.3%) having >75% signet-ring cell morphology. Lymphovascular invasion was present in 16 patients (53.3%), while perineural invasion was identified in 11 patients (36.7%).

Table 1

Baseline Patient Characteristics (n=30)

Characteristic	Value	
Demographics	Age, median (range), years	42 (28-67)
	Male gender, n (%)	18 (60.0)
	BMI, mean ± SD, kg/m ²	24.2 ± 3.8
Clinical	ECOG performance status 0, n (%)	23 (76.7)
	ECOG performance status 1, n (%)	7 (23.3)
Presentation	Distance from anal verge, median (range), cm	8.5 (4-14)
	Clinical stage II, n (%)	12 (40.0)
Staging	Clinical stage III, n (%)	18 (60.0)
	cT3, n (%)	21 (70.0)
	cT4, n (%)	9 (30.0)
	cN+, n (%)	18 (60.0)
Laboratory Parameters	CEA >5 ng/mL, n (%)	19 (63.3)
	CEA, median (range), ng/mL	12.4 (2.1-84.6)
	Signet-ring cells >75%, n (%)	22 (73.3)
Histopathological Features	Lymphovascular invasion, n (%)	16 (53.3)
	Perineural invasion, n (%)	11 (36.7)
	Grade 3 differentiation, n (%)	27 (90.0)

All 30 patients completed the planned induction chemotherapy with CapeOX for six cycles. Treatment modifications were required in 8 patients (26.7%) during induction therapy, primarily due to grade 2-3 peripheral neuropathy (5 patients, 16.7%) and grade 2 diarrhea (3 patients, 10%). No treatment discontinuations occurred during the induction phase. Following the planned 3-week interval, 29 patients (96.7%) proceeded to concurrent chemoradiotherapy. One patient developed disease progression during the interval period and was excluded from further analysis. Among the 29 patients who received concurrent treatment, 27 patients (93.1%) completed the full course of radiotherapy without treatment breaks. Two patients required radiotherapy interruption due to grade 3 dermatitis, resulting in treatment delays of 5 and 7 days, respectively.

Grade 3 or higher acute toxicities during concurrent chemoradiotherapy occurred in 9 patients (31.0%). The most common severe toxicities were dermatitis (4 patients, 13.8%), diarrhea (3 patients, 10.3%), and proctitis (2 patients, 6.9%). No grade 4 or 5 toxicities were observed during the treatment period.

Radiological assessment was performed at week 7 following completion of chemoradiotherapy in 29 patients. According to Response Evaluation Criteria in Solid Tumors version 1.1, 8 patients (27.6%) achieved partial response, 18 patients (62.1%) demonstrated stable

disease, and 3 patients (10.3%) showed progressive disease. Complete radiological response was not observed in any patient. Magnetic resonance imaging assessment revealed tumor downstaging in 14 patients (48.3%). T-stage downstaging occurred in 11 patients (37.9%), while N-stage downstaging was observed in 9 patients (31.0%). The median tumor volume reduction on magnetic resonance imaging was 32% (range 0-78%).

Table 2

Radiological Response Assessment (n=29)

Response Parameter	Value
RECIST 1.1 Response	
Complete response, n (%)	0 (0.0)
Partial response, n (%)	8 (27.6)
Stable disease, n (%)	18 (62.1)
Progressive disease, n (%)	3 (10.3)
MRI Assessment	
T-stage downstaging, n (%)	11 (37.9)
N-stage downstaging, n (%)	9 (31.0)
Overall downstaging, n (%)	14 (48.3)
Tumor volume reduction, median (range), %	32 (0-78)

Twenty-six patients (89.7%) proceeded to surgery at week 8 following chemoradiotherapy. Three patients did not undergo surgery due to disease progression (2 patients) and medical comorbidities (1 patient). Among the surgical candidates, low anterior resection was performed in 18 patients (69.2%), while abdominoperineal resection was required in 8 patients (30.8%).

Complete R0 resection was achieved in 23 patients (88.5%), while microscopically positive circumferential resection margins (R1) were identified in 3 patients (11.5%). No macroscopically incomplete (R2) resections occurred. The median number of lymph nodes harvested was 16 (range 8-28), with adequate lymph node sampling (≥12 nodes) achieved in 24 patients (92.3%).

Pathological complete response (ypT0N0) was observed in 4 patients (15.4%). An additional 6 patients (23.1%) achieved near-complete response with minimal residual disease (ypT1-2N0). Overall pathological downstaging occurred in 15 patients (57.7%), including T-stage downstaging in 12 patients (46.2%) and N-stage downstaging in 11 patients (42.3%).

Table 3

Surgical and Pathological Outcomes (n=26)

Outcome	Value	
Surgical Procedure	Low anterior resection, n (%)	18 (69.2)
	Abdominoperineal resection, n (%)	8 (30.8)
Resection Status	R0 resection, n (%)	23 (88.5)
	R1 resection, n (%)	3 (11.5)
Pathological Response	Pathological complete response (ypT0N0), n (%)	4 (15.4)
	Near-complete response (ypT1-2N0), n (%)	6 (23.1)
	T-stage downstaging, n (%)	12 (46.2)
	N-stage downstaging, n (%)	11 (42.3)
	Overall pathological downstaging, n (%)	15 (57.7)
Specimen Quality	Lymph nodes harvested, median (range)	16 (8-28)
	Adequate lymph node sampling (≥12), n (%)	24 (92.3)
	Tumor regression grade 3-4, n (%)	10 (38.5)

The overall incidence of grade 3 or higher toxicity throughout the entire treatment course was 40% (12 patients). During induction chemotherapy, grade 3

toxicities included peripheral neuropathy in 5 patients (16.7%) and diarrhea in 3 patients (10%). No grade 4 toxicities occurred during induction therapy. Concurrent chemoradiotherapy resulted in grade 3 acute toxicities in 9 patients (31.0%). The most frequent severe acute toxicities were radiation dermatitis (4 patients, 13.8%), diarrhea (3 patients, 10.3%), and radiation proctitis (2 patients, 6.9%). Post-operative complications within 30 days occurred in 7 patients (26.9%), including surgical site infection (3 patients), anastomotic leak (2 patients), and prolonged ileus (2 patients). No treatment-related mortality was observed.

Table 4*Treatment-Related Toxicity Profile*

Toxicity	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4-5, n (%)
Induction Chemotherapy (n=30)			
Peripheral neuropathy	15 (50.0)	5 (16.7)	0 (0.0)
Diarrhea	12 (40.0)	3 (10.0)	0 (0.0)
Fatigue	18 (60.0)	2 (6.7)	0 (0.0)
Hand-foot syndrome	8 (26.7)	1 (3.3)	0 (0.0)
Concurrent CRT (n=29)			
Radiation dermatitis	21 (72.4)	4 (13.8)	0 (0.0)
Diarrhea	16 (55.2)	3 (10.3)	0 (0.0)
Radiation proctitis	14 (48.3)	2 (6.9)	0 (0.0)
Fatigue	19 (65.5)	1 (3.4)	0 (0.0)

DISCUSSION

This prospective study provides current insights into the treatment response of rectal signet-ring cell carcinoma (SRCC) following neoadjuvant chemoradiotherapy (CRT). The pathological complete response (pCR) rate was 15.4%, and 57.7% of patients achieved pathological downstaging. Radiologically, 27.6% exhibited partial response per RECIST criteria, while 62.1% had stable disease and none achieved complete radiologic response. These findings reaffirm the limited responsiveness of SRCC to standard CRT, as consistently demonstrated in prior reports [1,10]. Previous studies have shown pCR rates between 10% and 23% in rectal SRCC [13,17], lower than the 20–30% pCR rates seen in conventional rectal adenocarcinomas, supporting its chemoradio-resistant nature [5,10].

Although tumor regression was limited, 88.5% of patients underwent successful R0 resection after chemoradiotherapy, and nearly 90% proceeded to surgery. This is notably higher than the 56% resectability rate reported by Engineer et al. (2015), where extensive infiltration often prevented curative surgery [1]. The higher conversion rate in this study may be linked to the use of induction CapeOX chemotherapy before radiation, following a total neoadjuvant therapy (TNT) model. Recent studies have supported TNT for improving tumor response and enhancing surgical outcomes [13,14]. Despite this approach, 42.3% of patients showed no nodal downstaging, and 10% progressed during treatment, reflecting the persistent therapeutic resistance characteristic of the signet-ring cell subtype.

The pathological complete response (pCR) rate of 15.4% observed in this study aligns with findings from other contemporary analyses of rectal signet-ring cell carcinoma (SRCC). Nadeem et al. (2024) reported no cases of pCR in

their SRCC group, with overall tumor regression significantly lower in signet-ring and mucinous tumors compared to typical adenocarcinoma [10]. Similarly, Zhang et al. (2019), through pooled analysis of three prospective trials, noted inferior responses in mucinous and signet-ring variants. In our data, 38.5% of patients exhibited moderate regression (TRG 3–4), while complete or near-complete responses remained rare [11]. This pattern reflects the mucin-rich histology of SRCC, which likely impairs effective chemoradiotherapy delivery. Although one Egyptian series reported a notably high pCR rate of 88.9% in SRCC (Attia et al., 2022), this finding diverges markedly from the broader literature [6,18]. Despite suggesting better tumor regression, that study reported no survival advantage, reinforcing the unpredictable behavior of SRCC and its limited responsiveness to conventional neoadjuvant strategies [8].

The clinical profile of patients in this study reflects established epidemiologic patterns of rectal signet-ring cell carcinoma (SRCC). A median age of 42 years and the predominance of advanced-stage disease (60% stage III at presentation) are consistent with prior reports describing SRCC as a distinct subtype affecting younger individuals and presenting with more locally advanced and nodal disease [4,5]. Despite multimodal therapy, the prognosis remains poor. While this study focuses on short-term outcomes, long-term survival in SRCC is historically limited. Wu et al. (2017) reported survival benefits with neoadjuvant radiotherapy; however, five-year survival remained below 30% [2]. In a matched cohort analysis, Gordeev et al. (2023) demonstrated a five-year survival of 34% in SRCC cases versus over 70% in non-SRCC, despite identical treatment protocols [3]. These findings underscore the urgent need for novel strategies to enhance outcomes in SRCC beyond the current standard of care.

Several biological features may explain the limited sensitivity of signet-ring cell carcinoma (SRCC) to chemoradiotherapy. These tumors are often poorly differentiated, rich in extracellular mucin, and exhibit early peritoneal dissemination, which impairs local treatment efficacy and contributes to high rates of incomplete resection or early recurrence [17]. Molecularly, SRCCs tend to be microsatellite stable and lack frequent mutations seen in other colorectal cancers, diminishing responsiveness to fluoropyrimidine-based regimens [15]. Recent genomic analyses have revealed distinct transcriptional signatures in SRCC, potentially offering future therapeutic targets. Immunosuppressive tumor microenvironments in mucinous variants may also suggest a role for immunotherapy. In a phase II trial, Yang et al. (2025) reported improved response when adding PD-1 inhibitors to chemoradiation, though most participants did not have SRCC. In our study, the intensified regimen was well-tolerated, with 97% completing therapy and R0 resection achieved in 88.5%, affirming feasibility despite aggressive disease [16,19].

This study has several limitations. Although it includes 30 patients, which is relatively large for rectal SRCC, the sample remains small due to the rarity of the disease. As a result, the findings may not detect smaller effects and should be interpreted cautiously. The follow-up period is

short, so long-term outcomes such as recurrence or survival could not be assessed. Being a single-center study, results may not reflect all clinical settings. Additionally, without a comparison group, the specific benefit of induction CapeOX chemotherapy remains uncertain, though supported by current recommendations for high-risk rectal cancer.

CONCLUSION

This study highlighted the aggressive nature of rectal signet-ring cell carcinoma and its suboptimal response to

conventional neoadjuvant chemoradiotherapy. Despite adherence to contemporary treatment protocols, including multimodal therapy and standardized surgical resection, the disease remains challenging in terms of early presentation and limited therapeutic responsiveness. These findings underscore the urgent need for tailored treatment strategies and long-term outcome assessments. Future trials focusing on novel systemic therapies and personalized regimens are essential to improve prognostic outlook in this uncommon subtype.

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