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ORIGINAL RESEARCH

Risk and Management of Bowel Obstruction in Colorectal Cancer Patients Undergoing Immunotherapy: A Cross-Sectional Multicenter Study

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Background: Despite the remarkable efficacy of immunotherapy for mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) colorectal cancer (CRC), patients may still develop bowel obstruction during tumor regression.

Methods: The study cohort included CRC patients who received immunotherapy at four medical centers. Bowel obstruction risk was assessed, and clinicopathological and molecular features were recorded. A Bayesian model was used to identify risk factors.

Results: A total of 214 patients were reviewed, with 196 patients meeting the eligibility criteria. Bowel obstruction occurred in 22 patients (10.3%) during immunotherapy. Obstruction was more commonly observed in patients with T4 stage tumors (P= 0.008), metastatic disease ($P < 0.001$), and an impassable lumen on baseline endoscopy ($P = 0.022$). Multivariable analysis revealed that T4 tumor was identified as an independent risk factor (odds ratios: 8.36, 95% confidence interval: 1.20–80.34). Among responders with obstructions, the median time to response was 6.1 weeks (interquartile range [IQR]: 5.5–10.7), the best response was 9.9 weeks (IQR: 5.6–23.6), and obstruction occurred at 6.6 weeks (IQR: 5.3–9.2). Notably, 42.9% (6/14) of the patients developed obstructions after laxative use during endoscopy. Four patients (18.2%) required surgery. Three (21.4%) patients in supportive therapy experienced recurrent obstructions. Four patients underwent endoscopic treatment (two stents, two balloon dilatations), all with symptom relief.

Conclusion: Bowel obstruction was common in CRC patients receiving immunotherapy. This risk may be suggested by two clinical features at baseline. Obstructions often occurred after the initial response but before the best overall response. Early detection and proper management may help to prevent or reduce obstructions.

Keywords: colorectal cancer, immunotherapy, bowel obstruction, risk factors, management

Introduction

Colorectal obstruction occurs in approximately 8–29% of patients at the time of colorectal cancer (CRC) diagnosis, and represents a major, potentially life-threatening complication that substantially impacts treatment decisions and patient outcomes.[1–3] Although certain clinical features, such as advanced stage or left-sided tumors, are known risk factors,[4–6] less is understood about how obstruction incidence and clinical presentation vary across molecular tumor profiles and contemporary treatment modalities, including immunotherapy.

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Immune checkpoint inhibitors (ICIs) target coinhibitory receptors such as PD-1, PD-L1, and CTLA-4, thereby enhancing immune cell activity against tumors; thus, these inhibitors represent effective and durable therapies for various types of cancer.[7,8] Mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) CRC represents a distinct subtype characterized by high immune cell infiltration and higher PD-L1 expression compared to MSI-L tumors, with no significant differences among different MSI-H molecular subtypes.[9–11] MSI-H tumors can be further classified into different subtypes based on the concordance of immunohistochemistry (IHC) results, a discrepancy that has been suggested to result from somatic mutations.[12] Multiple clinical trials have demonstrated that ICIs strikingly reduce tumor size and improve survival in patients with metastatic or locally advanced dMMR/MSI-H CRC.[13–16] In addition, genotypes with polymerase epsilon (*POLE*) or delta (*POLD1*) mutations have also been observed to be sensitive to ICIs in CRC patients, who typically exhibit microsatellite stable (MSS) and high tumor mutational burden (TMB-H).[17,18]

Despite the clinical benefits of immune checkpoint inhibitor therapy, the management of its toxicities and complications remains a critical issue.[19–21] In our previous studies, the risk of bowel obstruction was reported in 4–8% of patients who underwent immunotherapy for dMMR/MSI-H colorectal tumors.[22,23] Moreover, even for CRC patients who achieve significant regression with immunotherapy, fibrosis following the rapid shrinkage of bulky primary tumors may lead to obstruction.[24] Emergency surgical intervention is often necessary to alleviate this condition. Approximately 40% of emergency procedures may necessitate the creation of a stoma, which can impose considerable psychological distress on patients.[2] Therefore, early detection and appropriate management of bowel obstruction are important. However, the incidence and risk factors of this condition have not yet been demonstrated. With the widespread adoption of immunotherapy in patients with metastatic or locally advanced CRC,[16,25,26] a greater emphasis is needed on the management of the bowel obstruction.

This study focused on CRC patients undergoing immunotherapy and aimed to elucidate the incidence and risk factors for bowel obstruction, as well as explore appropriate clinical management strategies.

Methods

Study Design and Cohort

This cross-sectional study collected data from CRC patients who underwent immunotherapy between June 2019 and June 2024 at Sun Yat-sen University Cancer Center (SYSUCC), Jiangsu Cancer Hospital, Jilin Cancer Hospital, and the Affiliated Hospital of Southwest Medical University. The inclusion criteria involved the presence of primary tumors before immunotherapy and a molecular phenotype of either mismatch repair-deficient (dMMR), microsatellite instability-high (MSI-H), or tumor mutational burden-high (TMB-H, TMB $\geq$ 20 Mut/Mb).[27] The exclusion criteria included patients who had undergone ostomy or bypass surgery before immunotherapy, those who underwent surgery for non-obstructive reasons (such as perforations or fistula development) during treatment, and individuals lacking radiologic evaluations after immunotherapy. Data were obtained from the hospital's medical record system, as well as from endoscopy and radiology reports. The study was approved by the Institutional Review Board of SYSUCC (number B2023-697-01). Informed consent from the patients was waived due to the retrospective design of the study. This study adhered to the STROBE guidelines for observational studies.

Definition of Cases

The following definitions of colorectal obstruction were utilized: (1) confirmed obstruction, with radiologic and clinical evidence of obstruction and/or obstruction requiring urgent therapy in the hospital; and (2) symptomatic obstruction, wherein radiologic findings were inconclusive but clinical symptoms were consistent with obstruction and/or obstruction requiring surgical intervention.[28] Therefore, patients with complete obstruction or partial obstruction that met the above definitions were categorized into the obstructed group, while all others were assigned to the non-obstructed group for analysis. For patients presenting with multiple primary tumors, each tumor was analyzed as an independent case in the multivariable model. Shared patient-level characteristics (eg, age and sex) and tumor-specific variables (eg, tumor location and staging) were recorded accordingly.

MMR, MSI, and TMB Testing

All of the patients were required to have documented MMR, MSI, and TMB status. For patients who underwent tumor sequencing, MSI status and TMB levels were obtained from their reports. For other patients, MMR expression was assessed via immunohistochemistry (IHC), or MSI testing was performed by using polymerase chain reaction (PCR). Mismatch repair-deficient was determined by IHC as the loss of nuclear expression of at least one of the four mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) in tumor cells.[29] Microsatellite instability-high was defined as instability in two or more markers detected by PCR-based testing,[30] or as determined directly through tumor sequencing.

Immunotherapy Details

All of the patients were administered PD-(L)1 inhibitors due to the presence of colorectal tumors. These inhibitors included pembrolizumab, nivolumab, serplulimab, sintilimab, camrelizumab, toripalimab, tislelizumab and envafolimab, which were utilized either as monotherapies or in combination with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, targeted therapies, cytotoxic chemotherapy, or concurrent radiotherapy.

Clinical and Pathological Assessments

Clinical response was assessed via computed tomography (CT), magnetic resonance imaging (MRI), selective biopsies of suspected residual masses or scars, and digital rectal examinations for rectal cancer patients. The evaluation of tumor response was based on the RECIST criteria (version 1.1).[31] Following resection, tumor pathological response was determined by using the AJCC four-tiered grading system.[32] A pathological complete response was defined as the absence of viable tumor cells in the primary tumor bed and in all of the sampled regional lymph nodes.[33]

Statistical Analysis

Categorical variables are reported as frequencies and percentages, whereas continuous variables are presented as medians with interquartile ranges (IQRs). Associations between categorical variables were evaluated using the chi-square test or Fisher's exact test, whereas comparisons of continuous variables between groups were conducted via the Wilcoxon-Mann–Whitney test. All of the *P* values were two-tailed, with statistical significance set at $P < 0.05$. A Bayesian mixed-effects model was constructed for multivariable analysis with obstruction as the outcome.[34] Bayesian modeling is particularly suitable for studies in which the number of events of interest is relatively small (n = 22), as in this study. Weakly informative priors for fixed and random effects were specified to avoid implausible parameter values (Supplementary Methods 1 and Supplementary Figure 1). Model coefficients are presented as adjusted odds ratios (ORs) and 95% confidence intervals (CIs); these values can be interpreted in a similar manner to 95% C.I.s but are philosophically distinct.[35] Analyses were conducted using SPSS (version 27.0), the R Foundation Statistical Program version 4.3.3 and C-STAN (via the packages brms, finalfit, tidyverse, and bayesplot). Model diagnostics were assessed using *Shinystan*, trace plots, and posterior predictive checks (Supplementary Table 1 and Supplementary Figures 2, 3).

Results

A total of 214 CRC patients who underwent immunotherapy were reviewed, with 196 patients meeting the eligibility criteria and being included in the analysis. Overall, 22 patients (10.3%) developed obstructions during immunotherapy. The selection methods for this study are illustrated in Figure 1.

Baseline Characteristics and Risk Factors for Obstruction

Table 1 shows the characteristics of the obstructed and non-obstructed patients. Although more obstructions were observed in the ascending (27.3%) and transverse colon (22.7%), no significant differences were observed across tumor locations. Patients with advanced T stage disease exhibited higher rates of obstruction (T4 vs T2/T3, 15.5% vs 3.0%, respectively; $P = 0.008$), and metastatic patients demonstrated an increased risk of obstruction compared with nonmetastatic patients (IV vs I–III, 33.3% vs 8.1%, respectively; $P < 0.001$). Although an impassable lumen on baseline endoscopy was associated with a greater risk of obstruction (15.5% vs 4.9%, $P = 0.022$), no significant difference was

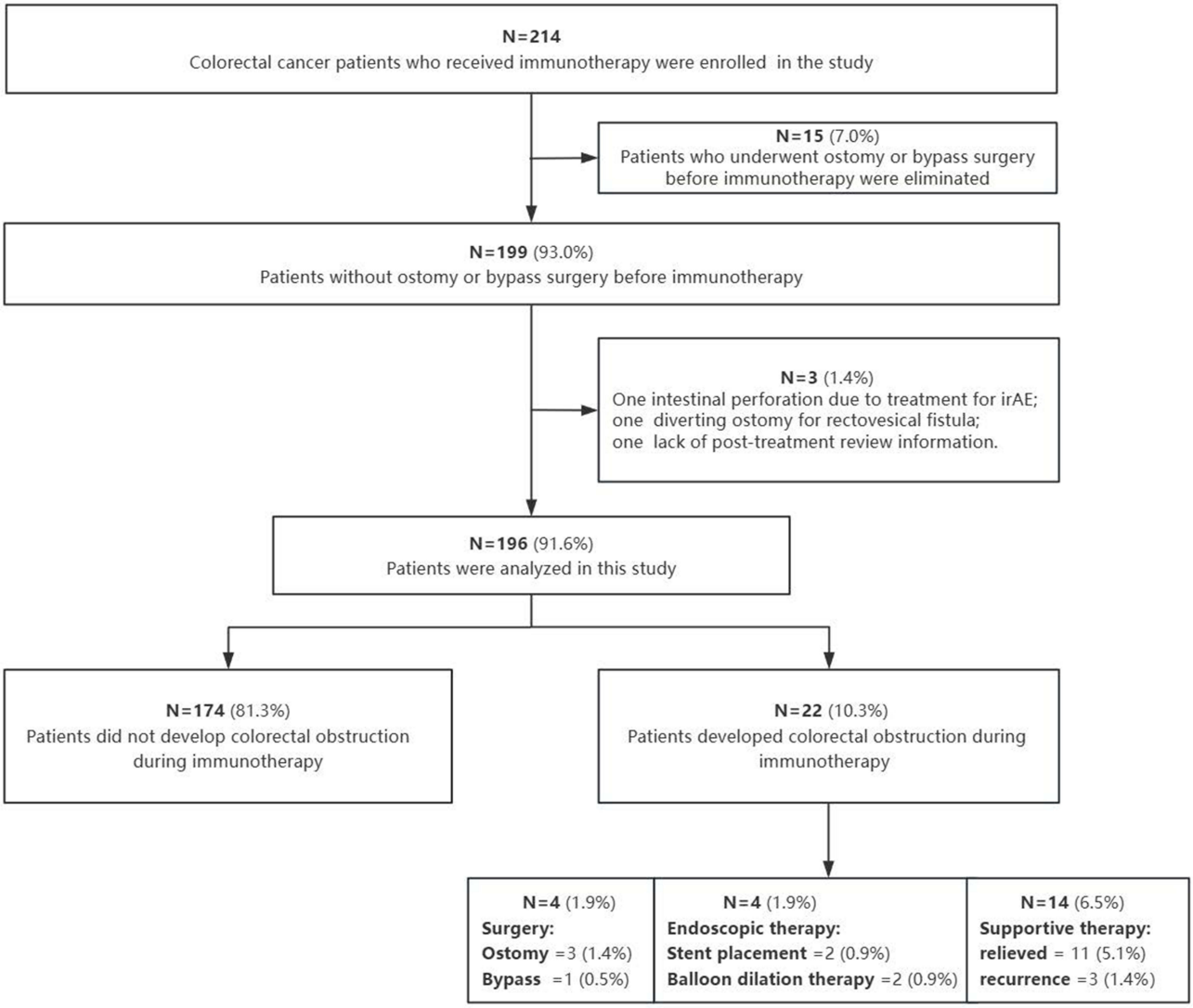

Figure 1 Flowchart of study patients. The classification of obstruction is based on different treatments undertaken at the first occurrence of obstruction, including surgery, endoscopic therapy and supportive therapy.
Abbreviation: irAE, immune-related adverse events.

observed in patients with circumferential infiltration on endoscopy. Moreover, there were no significant differences in pathological histology, degree of differentiation, or molecular features, such as RAS status and TMB levels.

A Bayesian mixed-effects model for multivariable analysis was constructed to identify significant risk factors in these patients. (Table 2). After adjusting for covariates, the radiographic T4 stage at baseline emerged as an independent risk factor for obstruction (OR: 8.36, 95% CI: 1.20–80.34). Additionally, an impassable lumen on baseline endoscopy was a borderline significant risk factor (OR: 5.52, 95% CI: 0.83–52.53) and was thus included in the subsequent analysis. Based on the tumor location, patients undergoing immunotherapy were classified into three risk categories (Table 3): low risk (<1%), intermediate risk (1–10%), and high risk (>10%).

Immunotherapy Efficacy in Patients with Obstructions

Table 4 presents a further analysis of the tumor response in obstructed patients. There were no significant differences observed in the treatment regimens that were used. However, the risk of obstruction was observed to be related to the clinical response in the radiologic assessments. Nonresponders (stable or progression disease, SD/PD) were observed to

Table 1 Baseline Characteristics Between Obstructed and Non-Obstructed Patients

Variables	Non-Obstruction n (%)	Obstruction n (%)	*P*
Total, n	174	22	
Age, Median (IQR), y	48.0 (37.0–60.0)	48.5 (34.3–55.8)	0.545
Sex			0.727
Female	78 (44.8)	9 (40.9)	
Male	96 (55.2)	13 (59.1)	
Tumor site			0.856
Ascending colon	43 (24.7)	6 (27.3)	
Hepatic flexure	19 (10.9)	3 (13.6)	
Transverse colon	28 (16.1)	5 (22.7)	
Splenic flexure	9 (5.2)	1 (4.6)	
Descending colon	11 (6.3)	1 (4.6)	
Sigmoid/rectosigmoid colon	15 (8.6)	3 (13.6)	
Rectum	38 (21.8)	2 (9.1)	
Multiple	11 (6.3)	1 (4.6)	
Clinical T stage			0.008
T2/T3	65 (37.4)	2 (9.1)	
T4	109 (62.6)	20 (90.9)	
Clinical TNM stage			<0.001
I–III	158 (90.8)	14 (63.6)	
IV	16 (9.2)	8 (36.4)	
Endoscopic pass			0.022
Able to pass	77 (47.0)	4 (20.0)	
Unable to pass	87 (53.0)	16 (80.0)	
Unknown	10	2	
Endoscopic circumferential infiltration			0.106
No	40 (30.1)	1 (6.7)	
Yes	93 (69.9)	14 (93.3)	
Unknown	41	7	
Histology			1.000
Adenocarcinoma	157 (90.2)	20 (90.9)	
Mucinous/signet ring carcinoma	17 (9.8)	2 (9.1)	
Tumor differentiation			0.761
Well/moderately differentiated	136 (78.2)	16 (72.7)	
Poorly differentiated	38 (21.8)	6 (27.3)	
RAS status			0.527
Wild-type	41 (44.6)	8 (53.3)	
Mutant-type	51 (55.4)	7 (46.7)	
Unknown	82	7	
TMB, median (IQR), muts/Mb	80.0 (51.9–113.7)	60.3 (51.9–82.6)	0.280

Note: χ^2 test calculations exclude unknown data.
Abbreviations: IQR, interquartile ranges; TMB, tumor mutational burden.

be associated with a greater risk of obstruction (38.1%), whereas responders (complete or partial response, CR/PR) exhibited a lower risk (8.0%).

Among the responders, the median time to response was 6.1 weeks (IQR: 5.5, 10.7), and the best overall response was observed at 9.9 weeks (IQR: 5.6, 23.6), whereas bowel obstruction occurred at 6.6 weeks (IQR: 5.3, 9.2; Figure 2). Notably, 42.9% (6/14) of these responders developed obstructions due to laxative use during the endoscopic examinations.

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Table 2 Bayesian Unconditional Mixed-Effects Model Demonstrating Features Associated with Obstruction

Variables	Odds Ratio	95% Credible Interval	
		Lower	Upper
Age[a]	0.61	0.21	1.56
Sex			
Female (Ref)	–	–	–
Male	1.32	0.21	8.92
Tumor location[b]			
Ascending or descending colon (Ref)	–	–	–
Hepatic or splenic flexure	0.65	0.05	6.90
Transverse colon	1.78	0.18	17.54
Sigmoid or rectosigmoid	2.14	0.19	24.24
Rectum	1.02	0.08	11.20
Clinical T stage			
T2/T3 (Ref)	–	–	–
T4a/T4b	**8.36**	**1.20**	**80.34**
Endoscopic pass			
Able to pass (Ref)	–	–	–
Unable to pass	5.52	0.83	52.53

Notes: Tumor locations were grouped anatomically by peritoneal covering of associated with the large bowel: sigmoid and transverse on a mesentery; ascending/descending colon retroperitoneal; flexures tethered; rectum extraperitoneal. Bold values indicate $P < 0.05$. [a]Age was standardized using z-score for modeling. [b]Patients with multiple primary tumors were analyzed separately (see Methods section).

Table 3 Estimated Risk of Obstruction in the 196 Patients Receiving Immunotherapy with or without Risk Factors

	Tumor Location				
	Ascending or Descending Colon	Hepatic or Splenic Flexure	Transverse Colon	Sigmoid or Rectosigmoid	Rectum
Non T4 stage AND able to pass scope	0.0% (0.0–0.0%) n=13	0.0% (0.0–0.0%) n=1	0.0% (0.0–0.0%) n=6	10.0% (1.8–40.4%) n=10	5.0% (0.9–23.6%) n=20
T4 stage (Radiology)	9.5% (2.7–28.9%) n=21	12.5% (2.2–47.1%) n=8	25.0% (4.6–69.9%) n=4	16.7% (3.0–56.4%) n=6	0.0% (0.0–0.0%) n=16
Unable to pass scope (Endoscopy)	0.0% (0.0–0.0%) n=7	0.0% (0.0–0.0%) n=7	14.3% (2.6–51.3%) n=7	0.0% (0.0–0.0%) n=6	0.0% (0.0–0.0%) n=2
T4 stage AND Unable to pass scope	20.0% (8.9–39.1%) n=25	16.7% (5.8–39.2%) n=18	16.7% (5.8–39.2%) n=18	28.6% (8.2–64.1%) n=7	33.3% (9.7–70.0%) n=6

Notes: Percentages show the proportion of tumors with bowel obstruction, with 95% confidence intervals in parentheses. N represents the estimated number of tumors in each group, based on data from 196 patients, including 12 patients with multiple primary tumors (see Methods). Predicted risk levels are indicated by color: white = low risk (<1%), light blue = intermediate risk (1–10%), dark blue = high risk (>10%).

Table 4 Therapy Details Between Obstructed and Non-Obstructed Patients

Variables	Non-Obstruction n (%)	Obstruction n (%)	*P*
Total, n	174	22	
Treatment regimens[a]			0.350
PD-1/PD-L1 alone	101 (58.4)	10 (45.5)	
Chemotherapy	13 (7.5)	4 (18.2)	
TKI	36 (20.8)	4 (18.2)	
CTLA-4	17 (9.8)	3 (13.6)	
Radiotherapy	6 (3.5)	1 (4.5)	
Radiotherapy combination			0.571
No	168 (96.6)	21 (95.5)	
Yes	6 (3.4)	1 (4.5)	
Clinical response			<0.001
SD/PD	13 (7.5)	8 (36.4)	
CR/PR	161 (92.5)	14 (63.6)	
Tumor resection			0.159
No	83 (47.7)	7 (31.8)	
Yes	91 (52.3)	15 (68.2)	
Pathological response			0.715
pCR	50 (55.0)	9 (60.0)	
Non-pCR	41 (45.0)	6 (40.0)	
Unknown	83	7	

Notes: [a]One patient combined with a COX-2 inhibitor in the non-obstruction group was excluded from the treatment regimens analysis. Among the patients who received radiotherapy, five received concurrent chemotherapy, one received anti-angiogenic therapy, and one received a CTLA-4 inhibitor. χ^2 test calculations exclude unknown data.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; pCR, pathological complete response; TKI, tyrosine kinase inhibitor.

Management of Patients with Bowel Obstructive or Stricture Disease

Table 5 provides detailed information on the obstructed patients. Four patients (18.2%) with obstructions required surgical interventions, including three ostomy procedures and one bypass procedure. Among these patients, three continued with immunotherapy, including two with a maintained response and one with stable disease (SD). Finally, tumor resections were performed in one responder and in one patient with stable disease, thus resulting in pathological assessments of pCR and non-pCR, respectively.

Among the remaining 18 patients, 14 (63.6%) initially received supportive therapy and were subsequently managed with a low-residue diet. Three patients (13.6%) on supportive therapy developed recurrent obstructions during treatment and required surgical interventions. Additionally, one patient with progressive disease (PD) underwent an ostomy, whereas two responders underwent tumor resections and achieved pathological CR.

Endoscopic treatment was performed in four patients (18.2%); specifically, two patients received stent placements, and two received balloon dilatation therapy (BDT). Patients who underwent stent placements continued with their treatment and subsequently underwent surgery, both of which involved pathological assessments of non-pCR. Notably, endoscopic BDT successfully relieved symptoms in two obstructed patients; moreover, one continued treatment with an ongoing response, whereas the other subsequently underwent surgery and achieved a pathological CR.

Endoscopic BDT was also applied to a patient who presented with pencil-thin stools without obstruction symptoms. This patient had T4-stage rectosigmoid colon cancer and developed a progressive luminal stricture after six cycles of immunotherapy. This patient's condition was successfully managed with prophylactic BDT, thereby allowing for endoscopic passage after eight cycles of treatment, followed by a watch-and-wait strategy (Figure 3).

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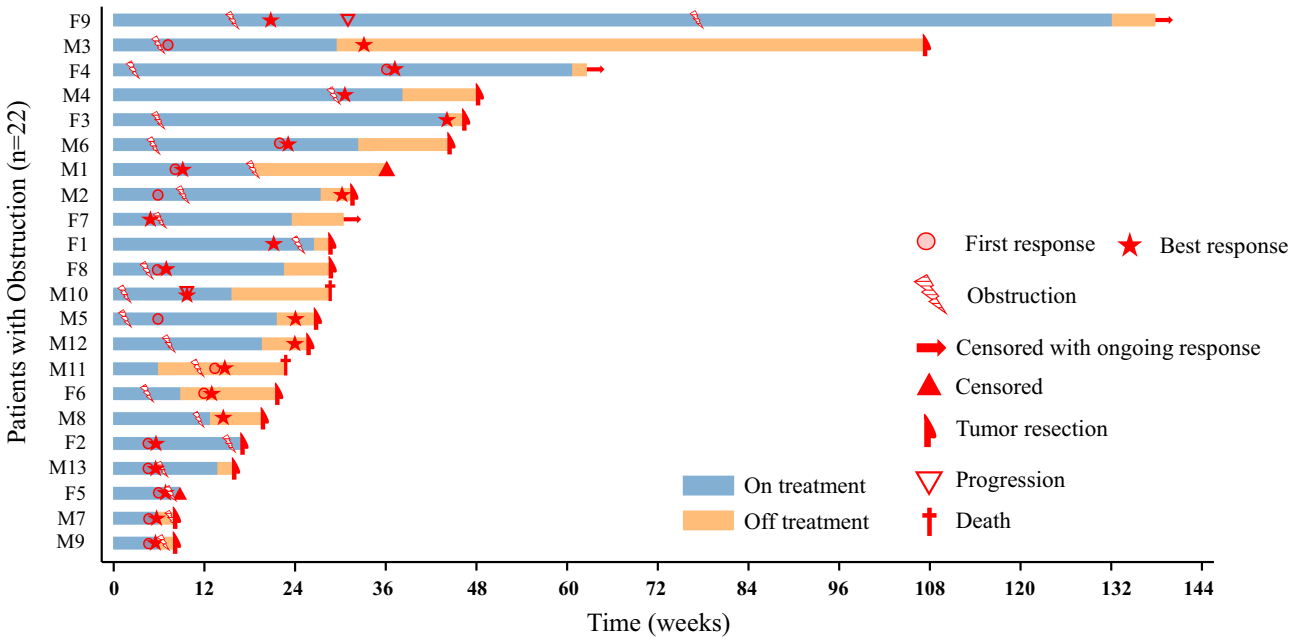

Figure 2 Swimmer plot of patients with bowel obstruction. Bars indicate the periods of immunotherapy treatment until events occurred (ie, resection, death or censoring). Fifteen patients underwent resection, two patients died, and five patients were censored.

Discussion

This study revealed a 10.3% incidence of bowel obstruction following immunotherapy in CRC patients. This risk may be associated with two baseline clinical features. These obstructions tended to develop following the tumor response but before achieving the best overall response during immunotherapy. Early detection and appropriate management can prevent the development and worsening of obstructions.

Although immunotherapy results in significant regression in dMMR/MSI-H colorectal tumors,[16,22,25] it demonstrates a greater risk of obstruction compared to conventional neoadjuvant chemotherapy in patients with locally advanced colon cancer, which was demonstrated in the FOxTROT study (10.3% vs 4.3%, respectively).[36] In this study, a high risk of obstruction was observed both in nonresponders (38.1%) and responders (8.0%). These findings indicate that bowel obstruction, which represents a previously neglected immune-related complication, should receive more attention during treatment.

The development of bowel obstruction during immunotherapy may be attributed to its distinct regression pattern. Unlike the scattered tumor regression induced by chemotherapy or radiotherapy, immunotherapy results in an "inside-out" (serosal-to-mucosal) regression pattern.[37] This distinct regression pattern may result in the formation of fibrous tissue. Residual fibrous tissue within the intestinal wall may contribute to stricture formation, thereby reducing the compliance of the intestinal lumen.[38,39]

These obstructions tended to develop after the initial tumor response but before achieving the best overall response was achieved during immunotherapy. Given the distinct regression pattern of immunotherapy and the delayed timing of its best response, the early phase of tumor regression (which exhibits increased fibrous tissue formation) results in a greater risk of obstruction. In this study, nine patients had tumors that were passable by endoscopy before immunotherapy; however, these tumors became impassable after treatment. This finding further supports the hypothesis that fibrous tissue formation following regression leads to obstruction.

Several studies have demonstrated that endoscopy provides a significant advantage in assessing CRC treatment efficacy,[40–42] thereby allowing for the earlier identification of CR compared to radiologic imaging in patients undergoing immunotherapy.[25] However, the current study revealed that obstructions developed in 31.8% (7/22) of the patients during bowel preparations for endoscopy in the early phase of treatment. Therefore, endoscopic assessments should be

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Table 5 Comprehensive Description of Clinical Characteristics, Causes, and Management in Patients with Bowel Obstruction

Patients	Tumor Site	T Stage	M Stage	Treatment	Inducement_ 1st	Management_1st	Subsequent Therapy	Obstruction Recurrence	Best Response	Inducement_ 2nd	Management_2nd	Tumor resection	Pathological response
F1	Rectum	T4b	M1	PD1+CT+RT	–	Supportive therapy	Continued	N	SD	–	N	Y	Non-pCR
M1	Ascending colon	T3	M1	PD1+CTLA-4	–	Supportive therapy	NA	N	PR	–	N	N	–
F2	Ascending colon	T4a	M0	PD1+TKI	Laxative	Supportive therapy	Continued	Y	PR	–	Tumor resection	Y	pCR
M2	Ascending colon	T4a	M0	PD1+TKI	–	Supportive therapy	Delayed	Y	CR	Laxative	Tumor resection	Y	pCR
M3	Transverse colon	T4b	M0	PD1+TKI	Laxative	Ostmy&bypass	Delayed	N	CR	–	N	Y	pCR
F3	Transverse colon	T4b	M0	PD1+CT+Cet +Darafenib	–	Supportive therapy	Continued	N	SD	–	N	Y	pCR
M4	Hepatic flexure	T4a	M1	PD1+CT+Bev	–	Endoscopic stent placement	Delayed	N	SD	–	N	Y	Non-pCR
F4	Ascending colon	T4b	M1	PD1	–	Ostomy	Delayed	N	PR	–	N	N	–
F5	Hepatic flexure	T4a	M0	PD1	Laxative	Supportive therapy	Continued	N	PR	–	N	N	–
F6	Rectum	T4b	M0	PD1	Laxative	Supportive therapy	Continued	N	PR	–	N	Y	Non-pCR
F7	Hepatic flexure	T4b	M0	PD1	Laxative	Endoscopic balloon dilatation	Delayed	N	SD	–	N	N	–
F8	Ascending colon	T4b	M0	PD1+CT	–	Supportive therapy	Normal	N	PR	–	N	Y	pCR
M5	Ascending colon	T4a	M0	PD1	–	Supportive therapy	Normal	N	CR	–	N	Y	pCR
M6	Sigmoid colon	T4b	M1	PD1+CTLA-4	–	Supportive therapy	Delayed	N	PR	–	N	Y	pCR
M7	Transverse colon	T4a	M0	PD1	–	Supportive therapy	Continued	N	PR	–	N	Y	pCR
M8	Sigmoid colon	T4a	M0	PD1	–	Endoscopic stent placement	Delayed	N	SD	–	N	Y	Non-pCR

(*Continued*)

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Table 5 (Continued).

Patients	Tumor Site	T Stage	M Stage	Treatment	Inducement_ 1st	Management_1st	Subsequent Therapy	Obstruction Recurrence	Best Response	Inducement_ 2nd	Management_2nd	Tumor resection	Pathological response
M9	Descending colon	T4b	M0	PD1	–	Supportive therapy	Continued	N	PR	–	N	Y	Non-pCR
M10	Splenic flexure	T4b	M1	PD1+CTX	–	Supportive therapy	Continued	N	PD	–	N	N	–
M11	Ascending colon	T4b	M0	PD1	–	Bypass	Discontinued	N	CR	–	N	N	–
F9	Transverse colon	T4a	M1	PD1+CTLA-4 +Cet +Vemurafenib	–	Supportive therapy	Continued	Y	SD	PD	Ostomy	N	–
M12	Sigmoid colon andrectum	T3	M0	PD1+CT	–	Ostomy	Delayed	N	SD	–	N	Y	Non-pCR
M13	Sigmoid colon	T4a	M0	PD1	Laxative	Endoscopic balloon dilatation	Delayed	N	PR	–	N	Y	pCR

Notes: M1–13 and F1–9 indicate individually numbered male and female patients. Delay in subsequent therapy is defined as postponement of immunotherapy for ≥7 days.

Abbreviations: CT, chemotherapy; RT, radiotherapy; TKI, tyrosine kinase inhibitor; Bev, Bevacizumab; Cet, Cetuximab; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; pCR, pathological complete response.

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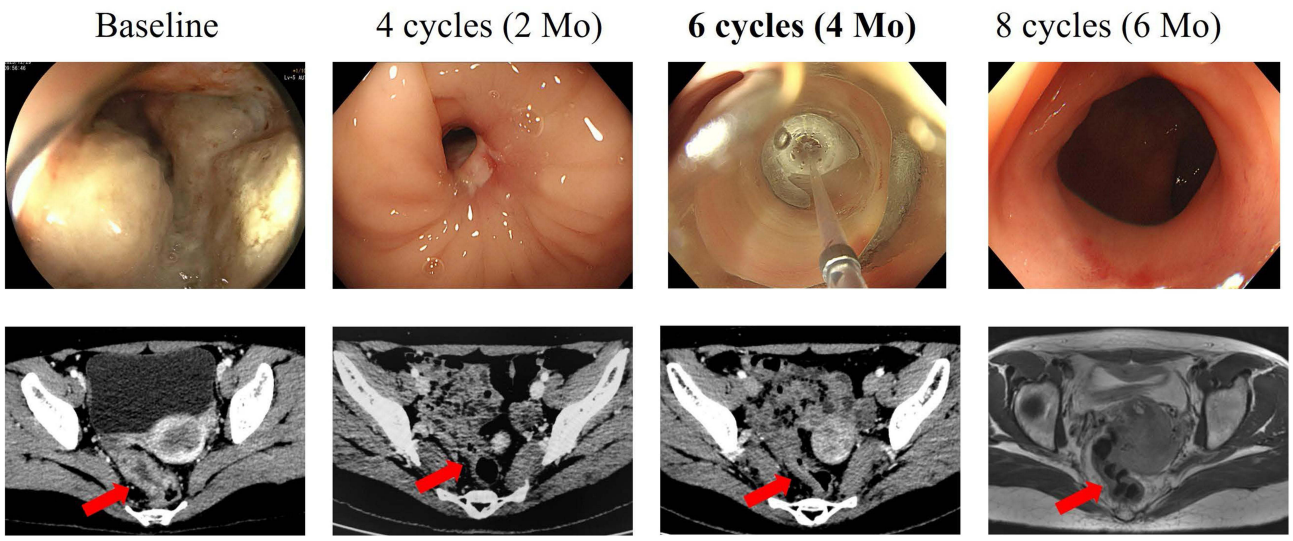

Figure 3 The patient developed a progressive luminal stricture following immunotherapy, which was successfully managed with prophylactic balloon dilatation therapy. Endoscopic and radiologic evaluations of the primary tumor were performed at baseline and at 2, 4, and 6 months, with the red arrow indicating the change of the primary lesion during treatment. Balloon dilatation therapy was conducted after six cycles of treatment (shown in bold in the figure), corresponding to the 4-month evaluation.

postponed. The optimal timing for endoscopic assessment may be after the best overall response has been determined via radiologic evaluation.

The management of obstruction during immunotherapy should be tailored to the specific treatment stage. For patients with severe obstructions who have not achieved their best responses, ostomy, bypass surgery, endoscopic stenting, or tumor resection are recommended,[5,43] followed by the continuation of immunotherapy. In cases where the best response has been achieved, tumor resection can be performed to confirm the pathological response and prevent the recurrence of bowel obstructions. Notably, endoscopic BDT has been identified as an effective option for patients with intestinal luminal strictures, as it causes less damage to the intestinal wall.[44] This study represents the first attempt to apply BDT to treat obstructions in patients undergoing immunotherapy, successfully alleviating the obstruction without complications. Recent studies have suggested that immunotherapy may serve as a potentially curative approach that could lead to organ preservation in patients with dMMR/MSI-H CRC,[22,25,45] and BDT could be a suitable treatment for patients who exhibit considerable regression but still experience obstructions. Given that this study revealed that fibrosis may gradually develop during immunotherapy, early detection and prophylactic endoscopic BDT in high-risk patients may prevent obstructions and ensure smooth treatment.

There are several limitations to this study. First, although this is a multi-center study, it remains susceptible to selection bias inherent to retrospective designs. Patient identification relies on existing medical records, which may vary in completeness and quality across center. Second, the lack of standardization in the treatment regimens, such as combinations with CTLA-4 inhibitors, chemotherapy, targeted therapies or radiotherapy, may affect the estimation of the incidence of obstruction caused by immunotherapy alone. Third, the small number of patients who developed obstruction resulted in limited statistical power. In particular, the extremely wide confidence interval observed for T4 stage indicates substantial imprecision and instability of this estimate, which may prevent firm conclusions regarding its role as a risk factor. Therefore, these results should be interpreted with caution. Finally, large-scale prospective studies are warranted to validate our findings, refine risk stratification, and establish standardized management strategies.

Conclusions

In summary, a high incidence of bowel obstruction was observed in CRC patients receiving immunotherapy. Two baseline clinical features, together with tumor location, may help estimate risk distribution. Most obstructions developed after the initial tumor response but before the best overall response was achieved. Considering the delayed best response time and the potential risks associated with laxative use, postponing routine endoscopic assessments during

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immunotherapy may be advisable. The management of obstruction should be individualized according to the specific treatment stage, and BDT may serve as a minimally invasive, safe, and effective option. Larger prospective studies are required to validate these observations, improve risk stratification, and establish standardized management strategies.

Abbreviations

BDT, balloon dilatation therapy; CRC, colorectal cancer; CR, complete response; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; dMMR, mismatch repair-deficient; ICIs, immune checkpoint inhibitors; irAE, immune-related adverse event; IQR, interquartile range; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OR, odds ratio; PR, partial response; SD, stable disease; PD, progressive disease, pCR, pathological complete response; TMB-H, tumor mutational burden-high.

Data Sharing Statement

The data that support the findings of this study are available from Dr Wu Jiang (jiangwu@sysucc.org.cn) upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (number B2023-697-01). It complied with the Declaration of Helsinki, and the requirement for informed consent was waived due to the retrospective nature of the study. Patient confidentiality was rigorously protected throughout the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Zhi-Gang Hong, Binyi Xiao, Muxu Zheng, Wanjun Yang, are co-first authors. Peirong Ding and Wu Jiang are co-senior authors.

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Disclosure

The authors report no conflicts of interest in this work.

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