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Smoking is a risk factor for postoperative ileus after radical resection in male patients

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Abstract

Most smokers are males, and smoking has been indicated as a risk factor for many cancers as well as postoperative complications after cancer surgery. However, little is known about whether smoking is a risk factor for postoperative ileus (POI) after radical rectal cancer resection in males. The aim of this study was to assess whether smoking is a risk factor for POI after radical resection in male rectal cancer patients.

Data of 1486 patients who underwent radical resection for rectal cancer were extracted from the clinical medical system in our hospital and were statistically analyzed. POI was defined as nausea, vomiting or pain, failure to have bowel function for more than 4 days postoperatively, and absence of a mechanical bowel obstruction.

The rate of POI was 12.79%. Univariate analysis showed that patients in the POI group were more likely to have a history of smoking and drinking and receive intraperitoneal chemotherapy and had a larger intraperitoneal chemotherapy dosage. In the multivariable analysis, smoking remained significantly associated with a higher incidence of POI (OR 2.238, 95% CI [1.545–3.240], $P = .000$). The results also showed that patients who received postoperative patient-controlled intravenous analgesia had a lower incidence of POI.

Male patients with a history of smoking who undergo elective radical resection for rectal cancer have an increased risk for POI complications.

Abbreviations: IP = intraperitoneal, PCIA = patient-controlled intravenous analgesia, POI = postoperative ileus.

Keywords: postoperative ileus, rectal cancer, risk factor, smoking

1. Introduction

Smoke was reported to be associated with an increased risk of many postoperative complications such as infections, pulmonary complications, wound complications, neurological complications, and general morbidity.[1–3] Postoperative ileus (POI) is one of the most common complications after rectal cancer surgery and is considered to be a type of gastrointestinal motility disturbance after colorectal cancer surgery. The definition of POI varies considerably, with a range of 1 to 7 days, a mean of 3.9 days and median of 4 days.[4] Approximately 15 factors may contribute to POI, including neurological factors, local inflammatory mediators, and surgical and anesthesia factors.[5–8] Only estimated blood loss and total postoperative opiate dosage have been shown to be independent risk factors associated with POI.[9] Study has reported smoking status is associated with POI after colon resection.[10] Little is known about whether pre-operative smoking effects POI after rectal cancer surgery in male patients. The aim of this study was to examine the association between POI and smoking in a large number of male patients who had undergone radical resection of rectal cancer to determine whether smoking is an independent risk factor for POI.

2. Patients and methods

In this retrospective study, we first obtained approval from the Ethics Committee of the Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital). This study was performed in accordance with the relevant guidelines and regulations of this committee. The need to obtain informed patient consent for this retrospective analysis of anonymized patient data was waived by the ethics committee who approved the study protocols. Second, data of 2929 patients who underwent rectal cancer surgery between January 2010 and July 2018 were extracted from the medical system of a tertiary cancer hospital. Pre-operative variables and data regarding POI

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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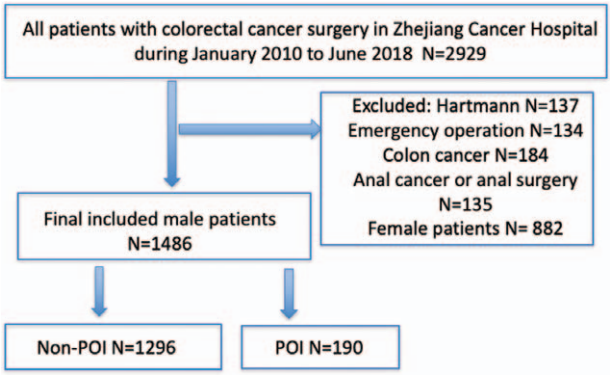

Figure 1. Flowchart of the included patients and study design.

were collected by surgeons, intraoperative variables were collected by anesthesiologists during surgery, and postoperative histopathological and diagnosis information was collected by pathologists. A total of 137 patients who had missing data, 134 who underwent emergency operations, 184 with colon cancer, and 135 with anal cancer or who underwent anal surgery were excluded. Thus, 1486 male patients among 2368 patients who underwent radical resection of rectal cancer were included in the final analysis. The participants included 837 male patients who smoked and 649 non-smoking male patients (Fig. 1). Patients who had a history of smoking more than 1 package per month before the operation were classified as smokers. The clinical details, perioperative variates, neo-adjuvant therapy, and postoperative pathological information of tumors were included. All resections were performed by a specialist in colorectal surgery in our hospital. POI was diagnosed if the patient had experienced nausea, vomiting or pain, failed to have bowel function for more than 4 days postoperatively, and did not have a mechanical bowel obstruction. Additionally, the tumor size and pathological information were extracted from the pathological system.

The pre-operative baseline patient characteristics included age, drinking, diabetes, hypertension, chronic heart disease, tumor stages, tumor size, nerve invasion, vessel invasion, and whether neo-adjuvant chemotherapy was received, and the intraoperative variables were surgery type, intraperitoneal (IP) chemotherapy, IP chemotherapy dosage, patient-controlled intravenous analgesia (PCIA), estimated blood loss, crystal volume, colloid volume, incidence of transfusion, transfusion volume, surgery duration, and urine volume. The dependent variable was POI.

2.1. Statistical analysis

The baseline patient characteristics and perioperative variables were compared between the POI and non-POI groups using a 2-sample independent t test for continuous variables or the Wilcoxon rank-sum test, depending on whether the underlying distribution was skewed. The Pearson $\chi 2$ test was used to compare categorical variables.

Multivariable logistic regression models were used to identify the association between 30-day POI and other possible risk factors. Variables that were statistically significant ($P < .05$); clinically important variables, such as operative duration, bleeding, IP chemotherapy incidence, and dosage, that are known as risk factors for POI; and variables that may have relatively small effects ($P \leq .2$) were included in the multivariable analysis. The covariates that were expected to confound the association between POI and smoking included drinking, PCIA, hypertension, laparoscopic surgery, IP chemotherapy, IP chemotherapy dosage, tumor stage, nerve invasion, and surgery duration.

3. Results

A total of 1486 patients were included in this study. Of whom, 837 patients (56.33%) were smokers. The mean age was 64.6 (±10.9) years in the POI group and 66.4 (±10.3) years in the non-POI group (Table 1).

The POI group had a higher incidence of IP chemotherapy (27.4% vs 19.2%; $P = .007$) and a larger IP fluorouracil dosage (220.5 ± 371.8 vs 156.4 ± 327.9; $P = .000$) than the non-POI group. Patients who received postoperative PCIA had a lower incidence of POI (73.3% vs 85.1%; $P = .000$). The estimated blood loss and other intraoperative variables were not significantly different between the 2 groups (Table 2).

After adjusting for confounders, smoking continued to be an independent predictive risk factor for POI (OR = 2.238, 95% CI, 1.545–3.240; $P = .000$). Patients in the PCIA group had a lower incidence of POI (OR = 0.514, 95% CI, 0.348–0.760; $P = .001$). Although the tumor stage is very important for long-term survival, prognosis and postoperative complications after radical resection of rectal cancer, the multivariable analysis results in this study showed that the tumor stage was not significantly associated with POI (Table 3).

4. Discussion

This study showed that smoking resulted in dramatic differences between the POI and non-POI groups. Previous studies have

Table 1

Baseline characters of patients undergoing radical rectal cancer resection. Which indicate that patients in the POI group were more likely to have a history of smoking and drinking. Continuous data were presented as mean ± SD and compared using the 2-sample Student *t* test or Wilcoxon rank-sum test. Categorical data were presented as incidence of the numbers (n [%]) of patients and compared using the Pearson chi-squared or Fisher exact test. Take $P < .05$ as significance.

		Male (1486)		
Variables		**Non-POI (1296)**	**POI (190)**	***P* value**
Age (±SD)		64.6 (10.9)	66.4 (10.3)	.203
HBP, n (%)		77 (5.9)	7 (3.7)	.136
DIA, n (%)		328 (25.3)	54 (28.4)	.203
CHD, n (%)		9 (0.7)	2 (1.1)	.591
Smoke, n (%)		698 (53.9)	139 (73.2)	.000
Drink, n (%)		527 (40.7)	95 (50)	.009
Tumor stage, n (%)				.179
	0	61 (4.7)	11 (5.8)	
	1	283 (21.8)	50 (26.3)	
	2	351 (27.1)	59 (31.1)	
	3	588 (45.4)	68 (35.8)	
	4	13 (1.0)	2 (1.1)	
Tumor size (±SD)		4.1 (1.9)	4.2 (2.7)	.482
Nerve invade, n (%)		222 (17.1)	36 (18.9)	.299
Vessel invade, n (%)		249 (19.2)	42 (22.1)	.199
Neo-adjuvant chemotherapy, n (%)		182 (14.1)	26 (13.7)	.924

CHD = coronary heart disease, DIA = diabetes, HBP = hypertension, POI = postoperative ileus, SD = standard deviation.

Table 2

Perioperative variables and postoperative of patients undergoing radical rectal cancer resection in POI and non-POI group. Patient in POI group were more likely to receive intraperitoneal chemotherapy and larger chemotherapy dosage during surgery. Patient who received PCIA have a lower incidence of POI.

Variables	Non-POI (1296)	POI (190)	*P* value
Estimated blood loss (±SD)	104.3 (105.2)	116.9 (100.4)	.351
Transfusion, n (%)	18 (1.4)	4 (2.1)	.307
Surgery duration (±SD)	178.7 (51.6)	183.9 (53.2)	.205
Surgery type, Laparoscopic, n (%)	245 (18.9)	43 (22.6)	.133
IP chemotherapy, n (%)	249 (19.2)	52 (27.4)	.007
IP chemotherapy Dosage (±SD)	156.4 (327.9)	220.5 (371.8)	.000
PCIA, n (%)	1103 (85.1)	140 (73.3)	.000
Crystal (±SD)	662.6 (256.7)	674.7 (249.2)	.951
Colloid (±SD)	478.1 (13.3)	479.2 (34.8)	.649
Urine (±SD)	457.4 (313.9)	494.7 (334.0)	.179

IP = intraperitoneal, PCIA = patient-controlled intravenous analgesia, POI = postoperative ileus, SD = standard deviation.

shown that smoking is an independent risk factor for postoperative outcomes after cancer surgery.[9,11,12] However, few studies have discussed the association between smoking and POI. Only 1 study found that smoking is associated with postoperative complications after colon resection in diverticulitis patients.[10] To the best of our knowledge, no previous study has included smoking in a multivariate analysis to determine whether it is a risk factor for POI after radical resection of rectal cancer in male patients. The present study is the first to show that smoking may be a risk factor for POI after radical rectal cancer resection. Based on this large single-center database, we found that most POI patients were male, and nearly all smokers were male in this study. We hypothesized that a history of smoking would result in an increased risk of POI after radical rectal cancer resection in the 1486 male patients. Previously reported POI rates after colorectal cancer surgery range from 4.3% to 15.9%.[13–16] The POI rate was 12.79% in this study.

There were significant differences between the smoking and non-smoking groups, indicating a pre-operative disparity in health status. The smoking group had a younger age and larger tumor size than the non-smoking group. Additionally, the smoking group had a higher incidence of IP chemotherapy and a lager fluorouracil dosage (Table 4). This may be partly due to the larger tumor size of the smoking group. Smoking has been shown to lead to poor outcomes for many cancers, but the mechanisms remain unclear.[16–19] Studies have shown that these effects may be due to the release of reactive oxygen species that cause damage at the cellular and tissue levels. Smoking also affects normal tissue perfusion,[20,21] impairs microcirculation,[22–24] increases oxidative stress, induces vascular injury,[25] reduces red blood cell velocity in the mesenteric vasculature and enhances venule pressure.[26] The decreased microcirculation and insufficient

Table 3

Multivariable analysis comparing covariates after rectal cancer radical resection in patient with and without POI.

Covariates	OR	95% CI	*P* Value
Age	0.980	0.965–0.996	.015
HBP	0.564	0.248–1.279	.170
DIA	1.145	0.796–1.647	.466
CHD	1.863	0.371–9.353	.450
Smoke	2.423	1.662–3.533	.000
Drink	1.044	0.744–1.464	.804
Neo-adjuvant Chemotherapy	0.937	0.566–1.553	.802
Laparoscopic	0.912	0.612–1.360	.651
Surgery Duration	1.000	0.996–1.003	.897
IP Chemotherapy	2.208	0.481–10.132	.308
IP Chemotherapy Dosage	1.001	0.999–1.003	.442
Estimated Blood Loss	1.000	0.998–1.001	.661
Transfusion	1.327	0.408–4.321	.638
Crystal Volume	1.000	0.999–1.000	.221
Colloid Volume	1.000	0.999–1.001	.944
Urine Volume	1.000	0.999–1.000	.532
Tumor Size	0.985	0.913–1.063	.695
Tumor Stage 0	0.675	0.121–3.756	.654
Tumor Stage 1	0.764	0.152–3.836	.744
Tumor Stage 2	0.929	0.185–4.649	.928
Tumor Stage ≥ 3	1.705	0.346–8.404	.512
Nerve Invade	1.494	0.957–2.334	.078
Vessel Invade	1.365	0.872–2.136	.174
PCIA	0.525	0.351–0.787	.002

CI = Confidence Interval, HBP = Hypertension, IP = intraperitoneal, OR = Odds Ratio, PCIA = Postoperative Patient-controlled Intravenous Analgesia

Table 4

Baseline characters and perioperative variables of patients undergoing radical rectal cancer resection. Which indicate that patients in the smoke group have a younger age, larger tumor size, have a higher incidence of postoperative ileus, and were more likely to receive intraperitoneal chemotherapy during surgery.

		Male (1486)		
Variables		Non-smoke (649)	Smoke (837)	*P* value
Age (±SD)		65.80 (11.60)	64.05 (10.24)	.002
HBP, n (%)		40 (6.16)	44 (5.26)	.261
DIA, n (%)		179 (27.6)	203 (24.3)	.082
CHD, n (%)		6 (0.92)	5 (0.60)	.333
Pathology, n (%)	0	34 (5.24)	38 (4.54)	.934
	1	148 (22.80)	185 (22.10)	
	2	181 (27.89)	229 (27.36)	
	3	280 (43.14)	376 (44.92)	
	4	6 (0.92)	9 (1.08)	
CEA (±SD)		20.92 (121.80)	20.47 (100.60)	.938
CA19-9 (±SD)		72.32 (421.94)	66.14 (345.90)	.757
CA72-4 (±SD)		4.55 (9.04)	5.41 (16.52)	.205
Tumor size (±SD)		3.97 (1.52)	4.27 (2.09)	.002
Nerve invade, n (%)		117 (18.03)	174 (20.79)	.103
Vessel invade, n (%)		118 (18.18)	140 (16.73)	.253
Neo-adjuvant chemotherapy, n (%)		87 (13.41)	120 (14.34)	.332
Estimated blood loss (±SD)		109.78 (108.69)	105.17 (102.75)	.406
Transfusion, n (%)		14 (2.16)	8 (0.96)	.046
Surgery duration (±SD)		176.30 (53.45)	181.78 (50.39)	.043
Surgery type, Laparoscopic, n (%)		533 (82.13)	665 (79.45)	.11
IP chemotherapy, n (%)		111 (17.10)	190 (22.70)	.005
IP chemotherapy Dosage (±SD)		132.67 (304.52)	189.37 (353.99)	.001
PCIA, n (%)		100 (15.41)	143 (17.08)	.213
Crystal (±SD)		1623.72 (484.26)	1676.81 (475.24)	.034
Colloid (±SD)		658.49 (250.23)	668.70 (260.06)	.446
Urine (±SD)		453.78 (315.32)	468.79 (318.06)	.365
Ileus, n (%)		51 (7.86)	139 (16.61)	.001

Continuous data were presented as mean ± SD and compared using the 2-sample Student *t* test or Wilcoxon rank-sum test. Categorical data were presented as incidence of the numbers (n [%]) of patients and compared using the Pearson chi-squared or Fisher exact test. Take $P < .05$ as significance.

CA19-9 = cancer antigen 19-9, CA72-4 = cancer antigen 72-4, CEA = carcinoembryonic antigen, CHD = coronary heart disease, DIA = diabetes, HBP = hypertension, IP = intraperitoneal, PCIA = patient-controlled intravenous analgesia, SD = standard deviation.

perfusion as well as vascular injury in patients with a history of smoking may contribute to POI after radical resection of rectal cancer; however, this hypothesis needs to be investigated in further studies.

Additionally, smoking was shown to reduce pulmonary barrier integrity and increase tumor growth.[27] Tobacco extracts have been demonstrated to promote cancer invasiveness in human colorectal adenocarcinomas and induce tumor angiogenesis and growth.[28,29] This retrospective study found that the smoking group had larger tumor sizes than the non-smoking group, which is consistent with previous conclusions.

This study identified smoking as an independent risk factor for POI after radical rectal cancer resection, which is another piece of strong evidence that smoking has a negative impact on health. There are several notable limitations of this study. First, this is a retrospective study. Second, this is a single-center study with only 1486 patients. Studies with a large number of patients or randomized controlled studies need to be performed to confirm these conclusions. Third, 2368 patients with radical resection of rectal cancer were initially included in this study, of whom, 1486 were male. There were 190 cases of POI among male patients and 30 cases among female patients. There were 837 smokers among male patients and 7 smokers among female patients. Therefore, most of the POI patients and most of the smokers were male. We aimed to determine whether any association existed between smoking and POI. However, this may lead to selection bias in this study. The results should be interpreted with these limitations in mind, and future prospective studies are needed to confirm the conclusions.

5. Conclusions

This study demonstrated that smoking is a risk factor for POI. Male patients with a history of smoking will have an increased risk for POI complications when undergoing elective radical resection for rectal cancer.

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Author contributions

WJL, CYF, and CXZ conceived of the study concept. GWJ, CXY, GY, SYJ, FM, LXY, GB, YJB, XYYZ, XKJ, and ZHD collected analyzed the data. WJL and CYF wrote the manuscript with support from ZHD and CXZ.

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