Effect and Safety of Intraoperative Intraperitoneal Chemotherapy on Patients Suffering From Colorectal Cancer.

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Abstract

Background

Colorectal cancer (CRC), the third most commonly diagnosed malignant neoplasm and the third most common cause of carcinoma-related mortality, continues to be a major international health problem. And approximately 33% of patients suffer from recurrence after radical surgery. Free malignant cells implanting in the peritoneum is generally accepted for present purposes. We did the study with the aim of evaluating the effects and safety of Intraoperative intraperitoneal chemotherapy (IOC) on patients suffering from colorectal cancer.

Methods

In total, 357 patients who went through colorectal radical surgery were considered eligible between September 23rd, 2017 to December 31st, 2018. 179 patients were treated with surgery alone, and 178 patients received surgery plus IOC. Clinical characteristics, operative findings, postoperative short-term outcomes and Disease- Free survival (DFS) were compared between the 2 groups in the selected population.

Result

The present research involves 357 patients (224 men and 133 women) who underwent surgery alone (n = 179) or surgery plus IOC (n = 178), with a mean (SD) age of 61.9 (10.4) years in the surgery alone group and 61.9 (9.1) in the surgery plus IOC group (P = .52). No significant differences were witnessed between the two groups in surgery-related information and postoperative complications. In patients with stage II colorectal cancer, the Disease- Free 1, 2and 3 years survival rates of surgery alone group were 98%, 91% and 86% respectively; and 96%, 94% and 81% respectively for surgery combined with IOC group (P = .82, Kaplan-Meier log-rank). In stage CRC patients, the survival rate analysis (Kaplan-Meier) showed a 82%, 68% and 61% Disease- Free survival of surgery alone group and a 94%, 85% and 82% of surgery plus IOC group after 1, 2 and 3 years, respectively (P = .002, Kaplan-Meier log rank).

Conclusions

In the present study, we have found that surgery plus IOC generated a favorable prognosis for stage CRC patients but not stage without any side-effects when the dosage of lobaplatin was 0.1 g/L. As a new, safe, and simple procedure, IOC therapy is easily performed anywhere and does not require any special devices or techniques. Thus, IOC is a promising and exciting therapeutic strategy for patients with CRC.

Introduction

Following lung and bronchus cancer and breast cancer in females and lung and bronchus cancer and prostate cancer in males respectively,Colorectal cancer, the third most commonly diagnosed malignant neoplasm and the third most common cause of carcinoma-related mortality continues a major

international health problem[1]. Although the total quantity of CRC is still the highest in Western countries; whose incidence and mortality pretend to be stabilizing or decreasing trends, and it is just the opposite in many developing countries, such as China[2]. Currently, radical resection remains the reference-standard treatment for early and even advanced cancer. The standard of care for CRC following radical resection is intravenous chemotherapy. Nevertheless, approximately 33% of patients suffer from recurrence after radical surgery[3]. Extraordinary, Peritoneal carcinomatosis, as a common type of CRC metastasis, has long been regarded as associating with poor prognosis for patients after radical surgery, and whose overall survival is even as poor as the multiple-organ metastases[4–6]. That might be relative to the insensitivity to systemic chemotherapy for peritoneal metastasis[7].

Free malignant cells implanting in the peritoneum is generally accepted for present purposes[8]. Consequently, it is necessary to kill the free malignancy cells before fixation on the peritoneum[9]. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has been recommended as an alternative approach for patients who have undergone R0 resection and resist cancer recurrence in the peritoneum[10]. However, it cannot be ignored that high morbidity and mortality restrict the application of HIPEC[11–13]. It's worth noting that opening lymphatic channels during operation might spread viable cancer cells into the abdominal cavity, which certainly provides evidence of the effectiveness of Intraoperative intraperitoneal chemotherapy[8]. Though intraoperative intraperitoneal chemotherapy, a new strategy to improve prognosis after R0 resection for CRC, has been confirmed valid[14], further research is needed about whether it can assuredly prolong overall survival (OS) time, prevent peritoneal metastasis following the radical operation and result in uncertain complications.

We did the study with the aim of evaluating the effect and safety of Intraoperative intraperitoneal chemotherapy on patients suffering from colorectal cancer.

Method

Patients

The retrospective study has met with approval by the ethics committee of Second Affiliated Hospital of Jilin University and performed in accordance with the Helsinki Declaration of World Medical Association, and the demand of patient informed consent was deserted because of the retrospective nature of this study. After rigorous screening, eventually, 357 patients who went through colorectal radical surgery were considered eligible between September 23rd, 2017 to December 31st, 2018. The baseline characteristics of the selected patients, consisting of age, gender, diabetic Mellitus, hypertension, tumor location, tumor size, pathologic T category, pathologic N category, TNM stage, degree of differentiation, tumor pathologic type, postoperative adjust chemotherapy and Carcinoma Embryonic Antigen (CEA) before the operation was carefully collected from medical records.

The intra and post-operation date, consisting of operation method, operation time, amount of intraoperative blood loss, time to first flatus, LOS (length of stay), abdominal pain and laboratory results (such as white blood cell count, neutrophil count, neutrophil-lymphocyte ratio, hemoglobin, albumin, and

albumin globulin ratio) 48 hours after the operation was also collected through consulting patients' medical notes. Follow-up information was obtained at an outpatient clinic of our center or using a telephone questionnaire directly. The final follow-up date for all of the cases was December 1st, 2020; and Disease-free survival (DFS) is defined as the time from radical operation to recurrence of tumor or death.

Visual Analogue Scale/Score (VAS), ranging from 0 to 10 (0, no pain; 1 to 3, mild pain [sustainable, sleep is not affected], 4 to 6, moderate pain [sleep is affected and painkillers are usually needed], 7 to 10, severe pain [Sleep is severely disrupted and painkillers are necessary]), was applied to evaluate the pain degree of postoperative patients[15]. In this study, the pain was defined as greater than 3 on the scale, considered to potentially affect emotional or physical functioning[16]. Postoperative complications (such as anastomosis or intra-abdominal bleeding, anastomosis leakage, abdominal cavity abscess, wound problems, Intestinal obstruction, lymphatic leakage, Cardiac disease, Deep vein thrombosis and Pulmonary disease) were evaluated by clinical manifestations, laboratory examination results, ultrasonography reports and imaging findings. Furthermore, massive hemorrhage was defined as an amount of at least 300 ml. Patients with albumin levels below 30 g/L were defined as hypoproteinemia.

Inclusion criteria

The inclusion criteria were showed as follows: 1) age between 18–80 y. 2) pathologically diagnosed as colorectal carcinoma. 3)TNM stage 2–3, proved through magnetic resonance imaging, CT (computerized tomography) or operation. 4)Patients underwent colorectal R0 resection.

Exclusion criteria

The following exclusion criteria applied to patients in this research: 1) Previous history of other systemic malignancies. 2)Receiving neo-adjuvant radiotherapy or neoadjuvant chemotherapy before operating. 3)Patients of familial adenomatous polyposis or human nonpolyposis CRC. 4)Severe respiratory tract, liver, kidney or cardiovascular disease. 5)patients going through emergency surgery. 6)The patients whose information cannot be collected accurately.

Surgical procedure

Bowel preparation was performed by taking Sulfate-free Polyethylene Glycol Electrolyte Powder orally one day before surgery. A standardized R0 surgical resection of colorectal carcinoma was then performed and all surgical procedures were conducted with strict adherence to the National Ministry of Colorectal Cancer diagnosis and treatment standards. Different procedures were selected according to the location of carcinomas. Laparotomy or laparoscopy was chosen according to intraoperative findings. Peritoneal lavage, as an important procedure was normally performed using 1000 ml 0.9% saline solution after intestinal anastomosis, which was then absorbed completely. Finally, the excised specimen was sent to professional pathologists to identify the TNM stage.

IOC

Lobaplatin was used for patients who underwent intraoperative intraperitoneal chemotherapy. 50 mg lobaplatin was dissolved in 500 ml 0.9% saline solution (SS) at a concentration of 0.1 g/L. The solution was then injected into an abdominal cavity through the drainage tube after the abdominal incision or laparoscopic port was closed. Vibrating abdomen adequately was routinely performed to make sure mixed solution distributing in the abdominal cavity evenly. Finally, the mixed solution was discharged from abdominal cavity 5 hours later. In the meanwhile, the drainage tube is closed to prevent the efflux of abdominal chemotherapy drugs.

Statistical Analysis

The study was designed to evaluate the superiority in terms of Disease-Free survival (DFS) of combining radical surgery and IOC compared with surgery alone. Survival curves were created using the Kaplan-Meier method, and the differences between the two groups were compared using *t* texts and χ^2 tests. All *P* values calculated in the analysis were 2-sided, and P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software, version 26.0 (IBM Corporation).

Results

From September 23rd, 2017 to December 31st, 2018, a total of 625 patients who underwent radical surgery for colorectal carcinoma in the Second Affiliated Hospital of Jilin University were collected, from which, 471 cases were selected to assessed ulteriorly according to the inclusion criteria. And 114 cases were eliminated on the basis of exclusion criteria (including 8 patients with Previous history of other systemic malignancies, 2 patients with familial adenomatous polyposis, 8 patients undergoing emergency surgery, 7 patients receiving neoadjuvant radiotherapy or neoadjuvant chemotherapy before operating, 4 patients with Severe respiratory tract, liver, kidney or cardiovascular disease and 85 patients' medical records unavailable) (Fig. 1). 357 cases were enrolled in the present study eventually, with 179 patients assigned to the surgery alone group and 178 assigned to the surgery plus IOC group.

The present research included 357 patients (224 men and 133 women) who underwent surgery alone (n = 179) or surgery plus IOC (n = 178), with a mean (SD) age of 61.9 (10.4) years in the surgery alone group and 61.9 (9.1) in the surgery plus IOC group (P = .52). Table 1 demonstrated that there was no statistical difference in the baseline clinical characteristics of the 357 patients between the two groups.

Table 1. Baseline Characteristics of patients

Characteristic	Patients, No. Surgery Alone (N=179)	Surgery Plus IOC (N= 178)	*P*-Value
Age, mean (SD), y	61.9(10.4)	61.2(9.1)	.52
Sex			
Male	106	118	.17
Female	73	60	
Hypertension			
Yes	40	49	.26
No	139	129	
Diabetic Mellitus			
Yes	27	31	.55
No	152	147	
CEA, mean (SD), ng/mL	9.90(16.02)	8.28(14.68)	.32
Tumor location			
Ascending colon	47	32	.17
Transverse colon	8	10	
Descending colon	12	6	
Sigmoid colon	30	35	
Rectal	82	95	
Tumor size, mean (SD), cm	4.9(1.7)	4.7(1.7)	.30
Pathologic T category			
T1	3	3	.68
T2	6	9	
T3	161	153	
T4	9	13	
Pathologic N category			
N0	95	88	.79
N1	61	65	
N2	23	25	

TNM stage			
□	95	87	.43
□	84	91	
Differentiation			
Well	6	4	.13
Moderate	168	161	
Poor	5	13	
Pathological type			
Tubular adenocarcinoma	171	165	.36
Mucinous adenocarcinoma	4	4	
Mixed adenocarcinoma	4	9	
Vascular invasion			
Yes	67	67	.97
No	112	111	
Postoperative chemotherapy			
Yes	115	100	.12
No	64	78	

Abbreviation: IOC, intraoperative intraperitoneal chemotherapy.

Surgery-related information is presented in Table 2. Laparoscopy surgeries were performed in a large proportion of patients (75.6%), 128 laparoscopy operations and 51 open surgeries were performed in the surgery alone group, and 142 laparoscopy operations and 36 open surgeries were performed in combining surgery and IOC group. No significant differences were observed between groups in operation methods, ASA stage, operation time and amount of intraoperation bleeding. Compared with the group of 179 patients receiving surgery alone, the group of 178 patients undergoing surgery plus IOC showed a similar trend in terms of Time to first flatus (73.7[11. vs 73.3[10.5]; difference, 0.4; 95%CI, -1.8-2.6; P = .72), LOS (19.7[7.0] vs 18.8[5.2]; difference, 0.9; 95%CI, -4.0-2.2; P = .17) and Postoperative laboratory results.

Table 2
Surgical Outcomes Following Surgery Alone or Surgery With IOC

Outcome	Mean (SD) Values	Surgery plus IOC	Between-Group Difference	P-Value
	Surgery alone (N = 179)	(N = 178)	(95% CI)	
Operation method, No. (%)	128(71.5)	142(79.8)	0.7(-11.6 to 12.9)	.07
laparoscopy		36(20.2)		.17
open surgery	51(28.5)	102(57.3)		.91
ASA	85(47.5)	72(40.4)		
□	90(50.3)	4(2.2)		
□	4(2.2)	213.8(54.1)		
□	214.5(63.0)			
operation time,min				
amount of intraoperation bleeding,ml	122(56)	117(55)	4(-7 to 16)	.47
Time to first flatus,h	73.7(11.0)	73.3(10.5)	0.4(-1.8 to 2.6)	.72
LOS,d	19.7(7.0)	18.8(5.2)	0.9(-4.0 to 2.2)	.17
Postoperative laboratory results	10.71(2.98)	10.29(2.41)	0.42(-0.14 to 0.98)	.15
White blood cell count, $\times 10^9$/L	8.89(3.04)	8.50(2.44)	0.39(-0.19 to 0.96)	.18
Neutrophil count, $\times 10^9$/L	0.823(0.077)	0.819(0.079)	0.004(-0.012 to 0.020)	.62
Neutrophil ratio	116(18)	119(21)	-3(-7 to 1)	.18
Hemoglobin, g/L	33.2(3.4)	33.6(3.3)	-0.4(-1.1 to 0.3)	.24
Albumin, g/L	1.36(0.21)	1.38(0.22)	-0.02(-0.06 to 0.02)	.38
Albumin globulin ratio				

Abbreviation: IOC, intraoperative intraperitoneal chemotherapy. ASA, American Society of Anesthesiologists. LOS, long of stay.

No perioperative deaths occurred both in the surgery alone group and the surgery plus IOC group (Table 3). No difference in abdominal pain was witnessed between the surgery alone group (83 of 179 patients [46.4%]) and surgery combined IOC group (79 of 178 patients [44.4%]) (difference, 2%; P = .71), nor in hypoproteinemia, anastomosis or intra-abdominal bleeding, anastomosis leakage, abdominal cavity abscess, wound problems, intestinal obstruction, cardiac disease, deep vein thrombosis or pulmonary disease. Clavien-Dindo classification[17] was used to assess the severity of postoperative complications. There was no significant difference between two groups in □/□ stage complications (97 [54.2%] vs 92[51.7%]; difference, 2.5%; P = .64) or □/□ stage complications (23[12.8%)] vs 14[7.9]; difference, 4.9%; P = .12).

Table 3
Postoperative Complications

Complication	**Patients, No. (%)** **Surgery alone** **(N = 179)**	**Surgery plus IOC** **(N = 178)**	***P*-Value**
Abdominal pain	83(46.4)	79(44.4)	.71
Hypoproteinemia	28(15.6)	23(12.9)	.46
anastomosis or intra-abdominal bleeding	2(1.1)	1(0.6)	1.00
anastomosis leakage	8(4.5)	3(1.7)	.22
Abdominal cavity abscess	7(3.9)	2(1.1)	.18
wound problems	24(13.4)	19(10.7)	.43
Intestinal obstruction	4(2.2)	3(1.7)	1.00
Cardiac disease	8(6.7)	8(4.5)	.99
Deep vein thrombosis	4(2.2)	3(1.7)	1.00
Pulmonary disease	11(6.1)	9(5.1)	.66
Clavien-Dindo classification	97(54.2)	92(51.7)	.64
□/□	23(12.8)	14(7.9)	.12
□/□	0	0	
□			

Abbreviation: IOC, intraoperative intraperitoneal chemotherapy. [a]The Clavien-Dindo classification scheme is explained in Dindo et al.[17]

In the present study, 64 patients had experienced a relapse or dead (surgery alone group, N = 40; surgery plus IOC group, N = 24) (Fig. 2), the Disease-Free Survival rates of surgery alone group were calculated by the Kaplan-Meier, with 90%, 80% and 75% at 1, 2, and 3 years, respectively; the Disease-Free Survival rates of surgery plus IOC group were 98%, 89% and 82% at 1, 2 and 3 years, respectively (P = .03, Kaplan-Meier log-rank). In patients with stage II colorectal cancer, the Disease- Free 1, 2and 3 years survival rates of

surgery alone group were 98%, 91% and 86%, respectively; and 96%, 94% and 81%, respectively for surgery combined with IOC group (P = .82, Kaplan-Meier log-rank), there was no significant differences between two groups (Fig. 3). In stage Ⅱ CRC patients, the survivorship analysis (Kaplan-Meier) showed an 82%, 68% and 61% Disease-Free survival of surgery alone group and a 94%, 85% and 82% of surgery plus IOC group after 1, 2 and 3 years, respectively (Fig. 4), which demonstrated that IOC was associated with a favorable prognosis in stage Ⅱ patients (P = .002, Kaplan-Meier log-rank).

Discussion

In recent years, the prognosis for Colorectal Cancer (CRC) performs more and more favorable with the development of diagnostic and treatment measures. However, the recurrence rate of patients who underwent curative resection for colorectal carcinoma was as high as 29.9%[18]. And peritoneal metastasis from colorectal cancer tended to perform an extremely poor prognosis. Remarkably, one survey revealed that the prognosis of the single-organ metastasis in the peritoneum group was even as poor as that of the multiple-organ metastases group[6].

Locally advanced colorectal cancer surgery, it should be noted, increases the risk of peritoneal metastasis because of the lymphatic opening caused by lymphatic clearance[8]. Therefore, if intraoperative intraperitoneal chemotherapy is put into effect, the viable malignancy cells resulting from destroyed lymphatic vessels may be eradicated and the prognosis would be better.

Here, we describe two main findings. First, when the lobaplatin concentration is 0.1 g/L, there is no significant difference between the intraoperative intraperitoneal chemotherapy group and the control group in short-term complications rate. Second, whether the IOC group is superior to the control group depends on the stage of CRC. For phase Ⅱ CRC patients, there is no distinct difference between the two groups in the terms of Disease-Free Survival (DFS); on the contrary, for phase Ⅲ CRC patients, the IOC group has significant advantages in Disease-Free survival (DFS).

Several randomized prospective studies[12 19]that evaluated the effect and safety of hyperthermic intraperitoneal chemotherapy (HIPC) as a therapy for peritoneal metastatic (PM) carcinoma have been published over recent decades. However, studies related to Intraperitoneal chemotherapy during operation for CRC patients without PM are quite rare.

There are two literature that evaluate the short-term efficacy of IOC in CRC patients. The study of the short-term effect analysis of intraoperative intraperitoneal perfusion chemotherapy with lobaplatin for colorectal cancer indicated that there is no distinction on short-term recovery between the study group and control group in patients with CRC, which was consistent with the result in the present study. However, Wang et al. indicated intraoperative intraperitoneal chemotherapy increases the incidence of anastomotic leakage after anterior resection of rectal tumors. The lobaplatin concentration in Wang's research was 0.12 g/L, which was higher than that in the present study, which may be the reason for the difference. Further studies are needed to verify whether IOC has an impact on postoperative anastomotic fistula for rectal malignant tumors. Moreover, one retrospective study evaluated the overall survival (OS)

in CRC patients undergoing IOC. The research of Intraoperative Chemotherapy with a Novel Regimen Improved the Therapeutic Outcomes of Colorectal Cancer enrolled 551 CRC patients, of which 193 patients underwent IOC. There was no significant difference in complication rate and mortality between the two groups, but the IOC group presented a better prognosis in phase Ⅱ and Ⅲ CRC patients compared with the control group. Those results were basically consistent with the result in the present research. However, in the present study, we found there would be no significant difference between the two groups in terms of prognosis if the CRC patients were at Ⅲ stage. The difference may result from the earlier T stage of patient in the present study. Of 182 stage Ⅲ CRC patients, 174(95.6%) patients were at T3 stage, and only 8(4.4) patients were at T4 stage. Leung V et al. presented that T4 stage identifies the majority of CRC patients who later develop PM[20]. Furthermore, in a prospective evaluation of the prognostic importance of peritoneal involvement in colonic cancer, N A Shepherd et al. enrolled 412 colorectal malignant tumor patients who underwent a primary resection and concluded that local peritoneal involvement is an independent predictive factor for intraperitoneal recurrence[21]. In addition, Jayne et al. found that 349 of 3019 patients with CRC have synchronous or metachronous PM, with 19% of the metachronous PM existing serosal invasion (stage T4)[5]. Therefore, intraoperative intraperitoneal chemotherapy should be recommended in patients with pT4 colorectal cancer. But the further study was needed to demonstrate the effectiveness of IOC for T4 stage patients.

In the present study, lobaplatin was used for interoperative intraperitoneal chemotherapy.

Lobaplatin, as a new generation platinum compound, has the same inhibitory effect on CRC

cells as oxaliplatin[22]. In addition, lobaplatin is appropriate for intraoperative intraperitoneal chemotherapy due to its lighter inhibitory effects on the neurological system, hematological system and gastrointestinal system. A preclinical model research[23] conduct that the survival rate of suspended CRC cells was only 16.3% when treated with 100 mg/L lobaplatin for 6 hours. Therefore, 0.1 g/L lobaplatin intraperitoneal chemotherapy for 6 hours during surgery was performed in order to obtain a strong efficacy on CRC patients with suspicious PM in the present study, while the dosage of 50 mg/person was far lower than the recommended dosage (50 mg/m2), without any obvious toxic side reaction.

The present study had several limitations. First, this is a retrospective comparison, unobserved confounders remained. An RCT would be idealized. Second, a sample size of the retrospective study was still small because the duration of implementing intraperitoneal perfusion chemotherapy was less than 5 years in Second Affiliated Hospital of Jilin University. But the study with a sample size of 357 patients was also acceptable. Third, our study involved only a Chinese population at a single center. Fours, there was no differences in the dosage of lobaplatin between CRC patients. Therefore, an individual chemotherapy regimen calculated by peritoneal area should be put forward through further study, though 50 mg/L lobaplatin had been confirmed safe and effective. In addition, a prospective and multi-center study with a large sample size is required in the future.

Conclusion

To our knowledge, only one study reported that IOC significantly improved the prognosis of colorectal cancer so far. In the present study, we found that surgery plus IOC generate a favorable prognosis for stage □ CRC patients but not stage □ without any side-effects when the dosage of lobaplatin was 0.1 g/L. As a new, safe, and simple procedure, IOC therapy is easily performed anywhere and does not require any special devices or techniques. Thus, IOC is a promising and exciting therapeutic strategy for patients with CRC.

Abbreviations

IOC: Intraoperative intraperitoneal chemotherapy;

CEA: Carcinoembryonic antigen;

CRC: Colorectal cancer;

DFS: Disease- Free survival;

CRS: Cytoreductive surgery;

HIPEC: hyperthermic intraperitoneal chemotherapy;

OS: overall survival;

LOS: length of stay;

VAS: Visual Analogue Scale/Score;

SS: saline solution;

ASA: American Society of Anesthesiologists;

PM: peritoneal metastatic.

Declarations

Availability of data and materials

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

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contributions

AS and MW conceived the study design. SW, YY, and LL acquired the data for the study. ZZ, DL, and YG analyzed and interpreted the data. AS drafted the manuscript. SW and YY revised the manuscript critically. The authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of The Second Hospital of Jilin University. Due to the retrospective design of the study, the local ethic committee confirmed that informed consent was not necessary from participants. The demand of patient informed consent was deserted because of the retrospective nature of this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

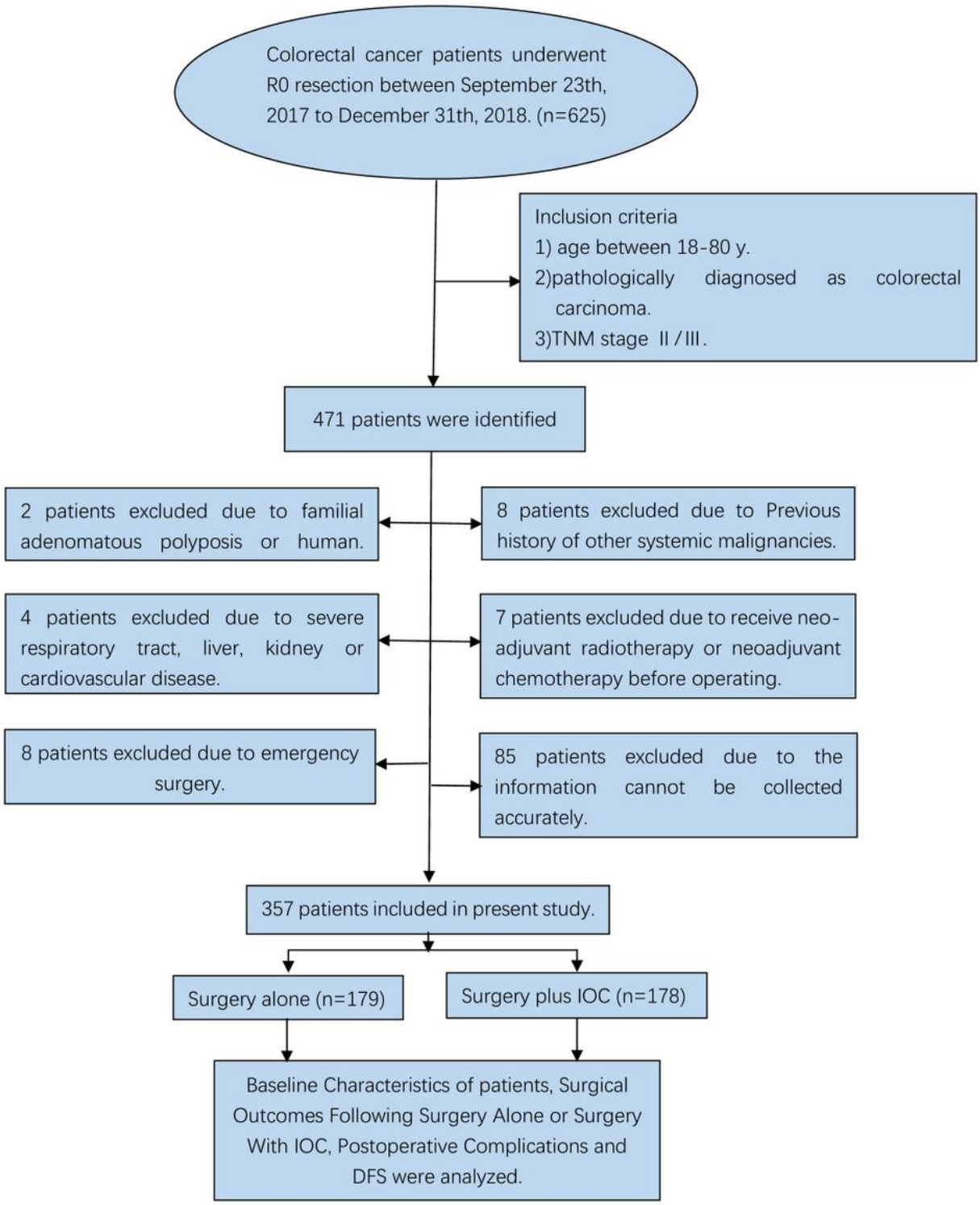

Figure 1

CONSORT Diagram of Patient Flow

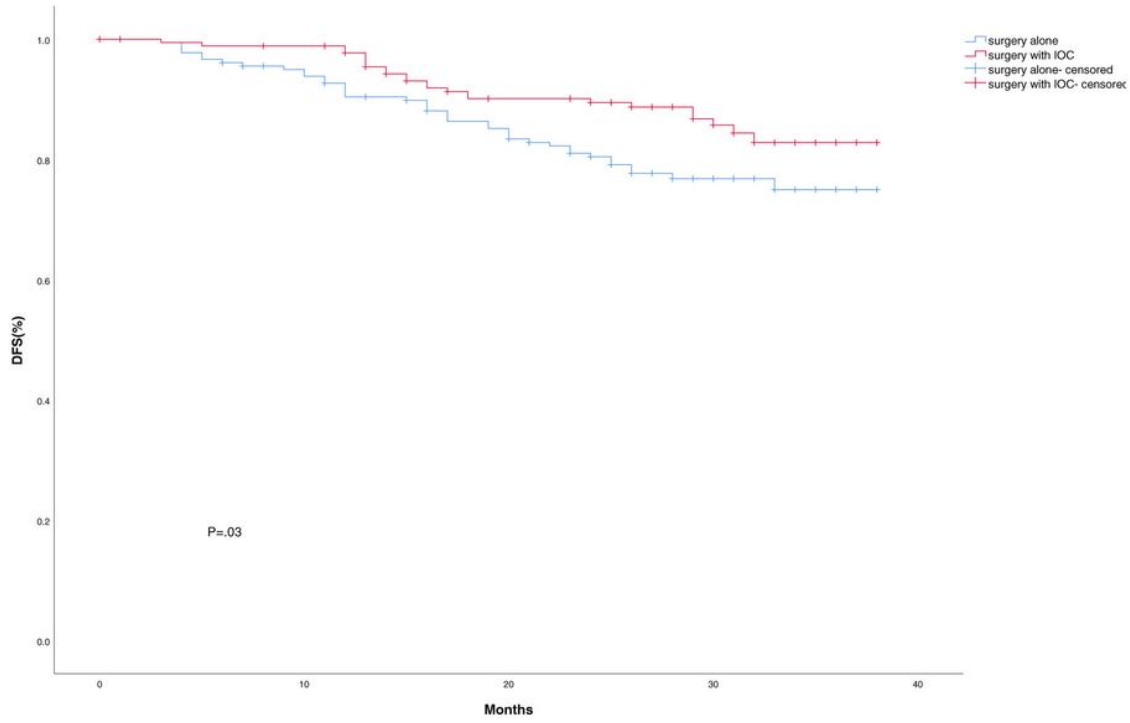

Figure 2

Disease-Free Survival outcomes following surgery alone or surgery plus IOC

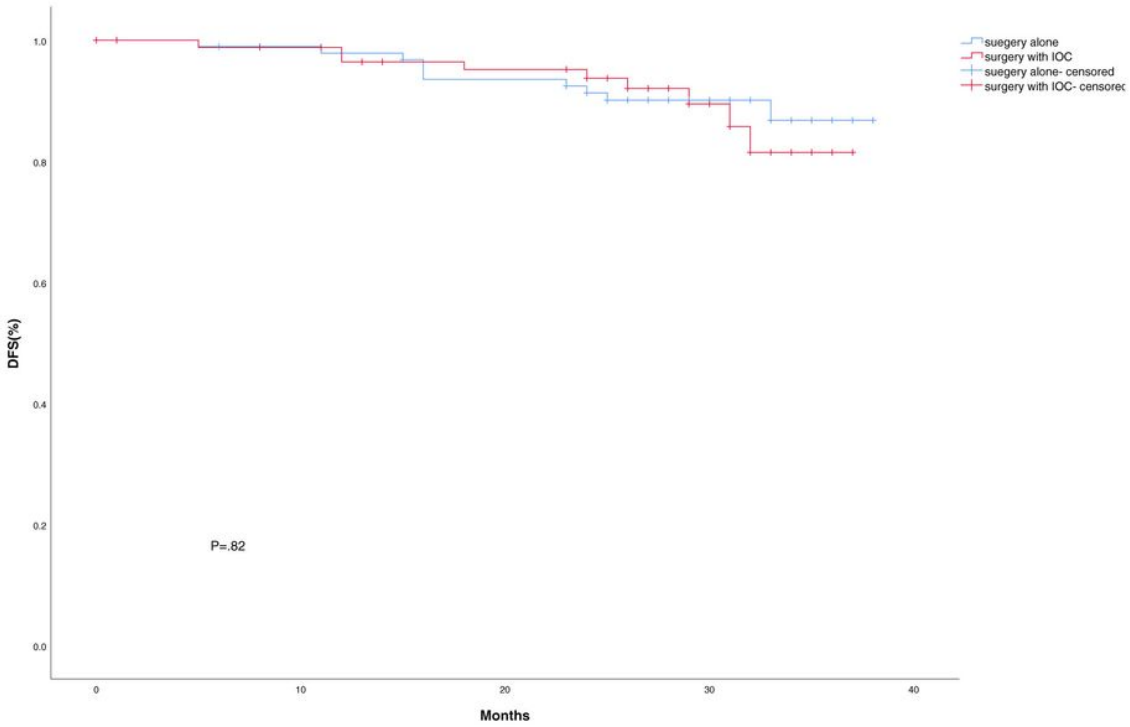

Figure 3

Disease-Free Survival outcomes following surgery alone or surgery plus IOC for stage patients

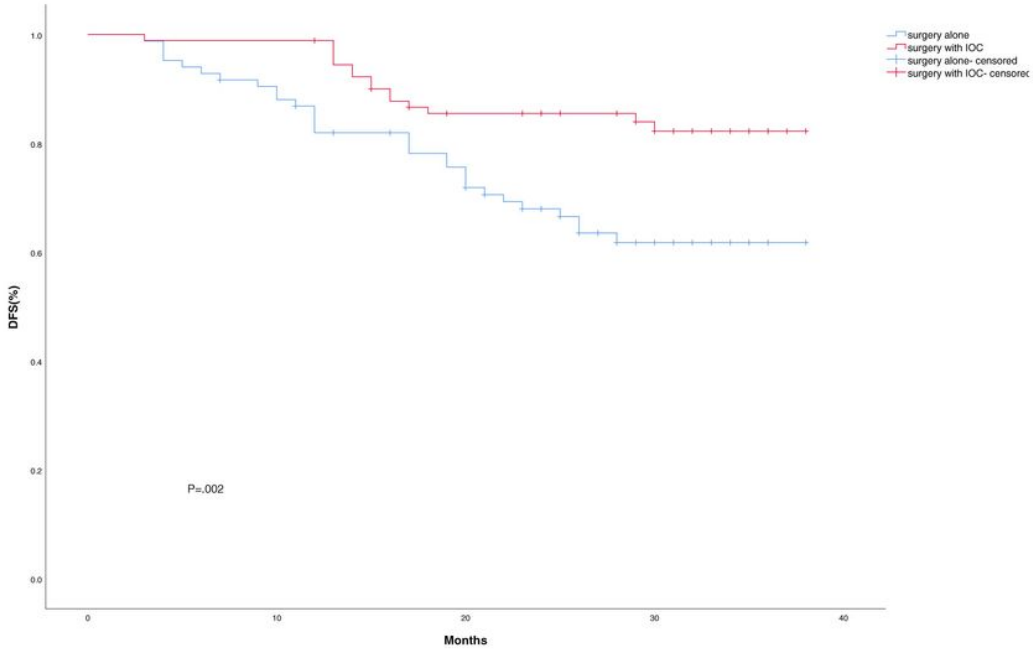

Figure 4

Disease-Free Survival outcomes following surgery alone or surgery plus IOC for stage patients