

# Stage II/III Rectal Cancer Patients Benefit from Extremely Early Initiation of Postoperative Adjuvant Chemotherapy: A Retrospective Study

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## Abstract

**Background:** For Stage II/III rectal cancer patients, curative resection is the primary treatment, prescribing of postoperative adjuvant chemotherapy (PAC) is regarded as a standard therapy. The interval between surgery and the initiation of PAC is usually within 8 weeks. However, the optimal cut-off is still controversial. This study aimed to explore the impact of extremely early initiation of PAC for II/III rectal cancer. **Methods:** Patients with Stage II/III rectal cancer treated from January 2013 to December 2015 were retrospectively collected at the Department of Tongji Hospital. According to the starting point of PAC, patients were categorized into two groups: extremely early group (The interval of PAC  $\leq$  2 weeks) and normal group (The interval of PAC within 3 - 5 weeks). For the sake of evaluating the effectiveness of different intervals, Overall Survival rate (OS), Progress-Free Survival rate (PFS) and Recurrence or Metastasis Rate (RMR) were analyzed, as well as the Quality of Life Score. To estimate the safety of the extremely early PAC, we evaluated the first post chemotherapy adverse reactions and defecation ability, and analyzed the variance laboratory indexes around the first postoperative adjuvant chemotherapy. **Results:** A total of 267 patients were included in this study. Compared to normal group (192 cases), extremely early group (75 cases) of patients attained a better tendency of OS and PFS, although there were no significant statistical differences (OS:  $P = 0.0930$ ; PFS:  $P = 0.1058$ ). However, the RMR was significant lower ( $P = 0.0452$ ) and the Quality of Life Score was significantly higher ( $P = 0.0090$ ) in extremely early group. Multivariate analysis also showed that extremely early group had better defecation ability ( $P = 0.0149$ ) and less side reactions of post chemotherapy, such as vomiting ( $P < 0.0001$ ), diarrhea ( $P = 0.0494$ ) or constipation ( $P = 0.0054$ ),

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meanwhile, got a higher level of inflammatory cells ( $P < 0.0001$ ) and a worse liver function ( $P = 0.0020$ ) before first chemotherapy. **Conclusion:** For Stage II/III rectal cancer patients, extremely early to start PAC not only might be effectively prolonging the survival, but indeed decrease the tumor-related recurrence risk, increase the quality of life and decrease chemotherapy-associated adverse reactions. Meanwhile, appropriately controlling of inflammatory cells and protecting the liver function should be of concern to ensure the safety of early initial stage.

### Keywords

Rectal Cancer, Postoperative Adjuvant Chemotherapy, Prognosis, Quality of Life, Chemotherapy-Associated Adverse Reaction

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## 1. Introduction

Rectal cancer is a very heterogeneous disease caused by the interaction of genetic and environmental factors [1], which is the third commonest cause of cancer and the fourth commonest cause of cancer death all over the world [2]. For Stage II/III patients, curative surgical resection remains the cornerstone of treatment, and postoperative adjuvant chemotherapy (PAC) is a standard treatment for Stage III as well as Stage II disease with risk factors [3]. A variety of studies have shown that postoperative chemotherapy significantly improves the 5-year survival rate and reduces the risk of recurrence or metastasis. Several models have documented that removing of primary tumor might lead to the deterioration of micrometastases, while postoperative systemic treatment would eradicate the accelerated growth of micrometastases [4]. Timely initiation of chemotherapy could be informed as the best available choice. Prescribing of chemotherapy should consider age, sex, underlying disease, economic status, and appearance of postoperative complications [5]. Updated international guidelines recommend that maximum interval from the development of a management plan to chemotherapy initiation is 12 weeks for PAC. Most clinical trials mandate the initiation of adjuvant chemotherapy for surgically resected colorectal cancer within 4 - 8 weeks post-surgery [6]. A large, randomized study conducted with Stage II/III CRC patients in the Hospital Episode Statistics (HES) reported that PAC initiation beyond 8 weeks significantly reduced overall survival (OS) in patients, compared to those who received it within 8 weeks, and every 2 weeks increments in the delay accompanied by progressively worse OS [7]. This viewpoint was in accordance with a meta-analysis published in 2010, which concluded that delaying of initiation more than 8 weeks was associated to a worse OS but not a worse Relapse-Free Survival (RFS) [3]. However, there is no clear consensus with the optimal time of initiating PAC, let alone the extremely early initiation of PAC, since clinicians worry about the side effects induced by the agents of chemotherapy [8]. Researches about the quality of life and the safety are also scarce in ear-

ly adjuvant chemotherapy group.

Our study therefore aims to quantitatively compare the effectiveness and security of extremely early PAC group to normal in Stage II/III rectal cancer patients, utilizing 3 years epidemiological data of patients undergoing radical rectum resection.

## 2. Methods

### 2.1. Population Definition

From January 2013 to December 2015, patients underwent selective curative surgery were retrospectively collected at department of General Surgery in Tongji Hospital. All information about patients, such as tumor characteristics, diagnosis and treatments were conventionally extracted from the medical records. Selected criteria were following: 1) postoperative pathological examination had confirmed for stage II ( $T_{3-4}N_0M_0$ ) or stage III ( $T_xN_{1-2}M_0$ ); 2) circumferential margins were negative; 3) further chemotherapy had been accepted; 4) no obvious nausea vomiting diarrhea or constipation; 5) regular diets had established; 6) anus or stoma had returned to normal flatus and defecation; 7) nutritional examination indexes had reached a normal level. Exclusion criteria: 1) refused to accept any chemotherapy after surgery; 2) preferred to have a longer interval for recovery; 3) received neoadjuvant chemotherapy or chemoradiotherapy; 4) severe anemia or neutropenia; 5) diets or defecation had not regularly built; 6) nutritional condition could hardly tolerate chemo-associated toxicity. In our hospital, the regimens and initiation of all PACs were decided by the surgeons with medical oncologists. The objects in this study were divided into two groups: extremely early group (The interval of PAC  $\leq 2$  weeks in 75 cases) and normal group (The interval of PAC within 3 - 5 weeks in 192 cases). The demographic characteristics of patients were collated by two individuals, which were shown in **Table 1**. All patients volunteered to participate in this clinical investigation, and ethics committee approved this consent procedure as well.

### 2.2. Surgery, Postoperative Adjuvant Chemotherapy, and Follow-Up

After a fully preoperative preparation, all patients underwent standard surgical procedure, which performed total mesorectal excision (TME) by open or laparoscope-assisted surgery. The major operation methods consisted of low anterior resection (Dixon), abdominoperineal resection (Miles), resection of abdominal rectal cancer, proximal colostomy, and distal closure (Hartmann).

After recovery from surgery, all patients with stage II/III were recommended to receive a total of approximately 6 months postoperative chemotherapy according to National Comprehensive Cancer Network (NCCN) Guidelines. Specific chemotherapy regimens: Oxaliplatin 85 mg/m<sup>2</sup> IV day 1, Leucovorin 400 mg/m<sup>2</sup> IV day1, 5-Fluorouracil 400 mg/m<sup>2</sup> IV bolus day 1, then 1200 mg/m<sup>2</sup>/d  $\times$  2 days (total 2400 mg/m<sup>2</sup> over 48 hours) continuous infusion, repeat every 2

weeks (mFolfox-6); Oxaliplatin 130 mg/m<sup>2</sup> IV day 1, Capecitabine 1000 mg/m<sup>2</sup> twice daily 1 - 14 every 3 weeks, repeat every 3 weeks (CapeOX); Capecitabine or Tegafur 1000 mg/m<sup>2</sup> twice daily 1 - 14 every 3 weeks, repeat every 3 weeks (Monotherapy). Time to PAC was defined the interval from the surgery to the first initiation of chemotherapy.

All patients were enrolled in an appointed database and followed at 3 month intervals for the first years, 6 month intervals for the second year and 9 month intervals for the third year. Computed Tomography (CT) scan checked 4 times the first year, 2 times the second year and once a year after. Enteroscopy checked once a year. The primary endpoint was oncological death or recurrence, while the secondary endpoint was the present quality of life.

**Table 1.** Baseline demographic characteristics of rectal patient cohorts who received PAC after curative resection of Stage II or III.

Characteristics	Timing of postoperative adjuvant chemotherapy		P value
	≤2 weeks (n = 75)	3 - 5 weeks (n = 192)	
<b>Gender</b>			
Male	45	118	0.8891
Female	30	74	
<b>Age</b>			
≤60 years	50	137	0.4606
>60 years	25	55	
<b>T stage</b>			
T1	15	34	0.3541
T2	7	31	
T3	53	127	
<b>N stage</b>			
N0	42	96	0.2278
N1	16	61	
N2	17	35	
<b>TNM</b>			
Stage II	38	90	0.5886
Stage III	37	102	
<b>Tumor grade</b>			
Well/Moderate differentiation	46	138	0.1065
Poor differentiation	29	54	
<b>Specific chemotherapy regimen (may changed during the cycles)</b>			
mFolfox-6	37	51	0.2615
CapeOX	28	130	
Monotherapy	16	18	

### 2.3. Outcome Measurements

Overall Survival (OS) was calculated conventionally from the date of operation. Progress-free survival time (PFS) was defined the interval between the operation and the first diagnosis of recurrence or metastasis. Recurrence and Metastasis Rate (RMR) was counted for whole percentage of recurrence or metastasis. About the quality of life, we adopted the Eastern Cooperative Oncology Group-performance status (ECOG-PS) [9], which evaluated the quality as 0 - 4 points. We suggested 0 - 1 point as a better lifestyle,  $\geq 2$  point prompted a worse. To chemotherapy-associated adverse reaction, we chose vomiting, diarrhea and constipation for delegation. Those who without chemotherapy associated diarrhea and constipation were defined as a better defecation ability of anus or stoma. Multiple indexes around the first PAC, such as white blood cell (WBC), neutrophils (N), glutamic pyruvic transaminase (GPT), glutamic oxalacetic transaminase (GOT) and albumin (ALB) were counted in paired groups.

### 2.4. Statistical Analysis

All statistical analyses used Graphpad Prism 6.0. Categorical variables were analyzed using a Chi-squared test or Fisher's exact test. Continuous variables were described as mean and standard deviation, and analyzed by unpaired t test. Survival curves were plotted using the Kaplan-Meier method with Log-rank test and Hazard Ratio model. Statistical significance was indicated as  $p < 0.05$ .

## 3. Results

We collected data from 612 patients with Stage II ( $n = 326$ ) and Stage III ( $n = 286$ ) illnesses during 2013 to 2015, among them, 104 patients did not receive chemotherapy. Within 508 patients with adjuvant chemotherapy, we removed some data that included 189 patients starting chemotherapy 6 weeks or more after surgery and 52 patients of receiving neoadjuvant chemotherapy or chemoradiotherapy. The remaining 267 patients with Stage II/III rectal cancer, who had undergone radical resection and postoperative adjuvant chemotherapy, were divided into pairing groups at a ratio of 1:2 (case vs. control). Mean age of the population was fifty-four years old, thirty percent of whom were older than sixty, and the proportion of male and female was approximately 1.5:1. As a whole, there was no significant difference in gender or age between two groups. Besides, oncological characteristics, such as T stage, N stage, TNM stage or tumor grade also showed no statistical significant between. Additionally, after critical paired selection, neither of specific chemotherapy regimens between showed any difference. Generally speaking, there was a potential comparability between two groups without any obvious biases. For extremely early group, the median timing of PAC was 10 days, while, the control group was 28 days (**Figure 1**).

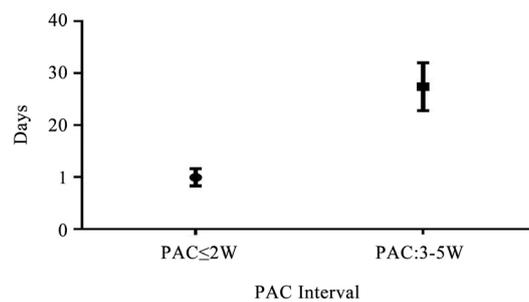
### 3.1. Long-Term Survival and PAC Interval

During the subsequent follow-up, a total of 32 participants lost their follow-up

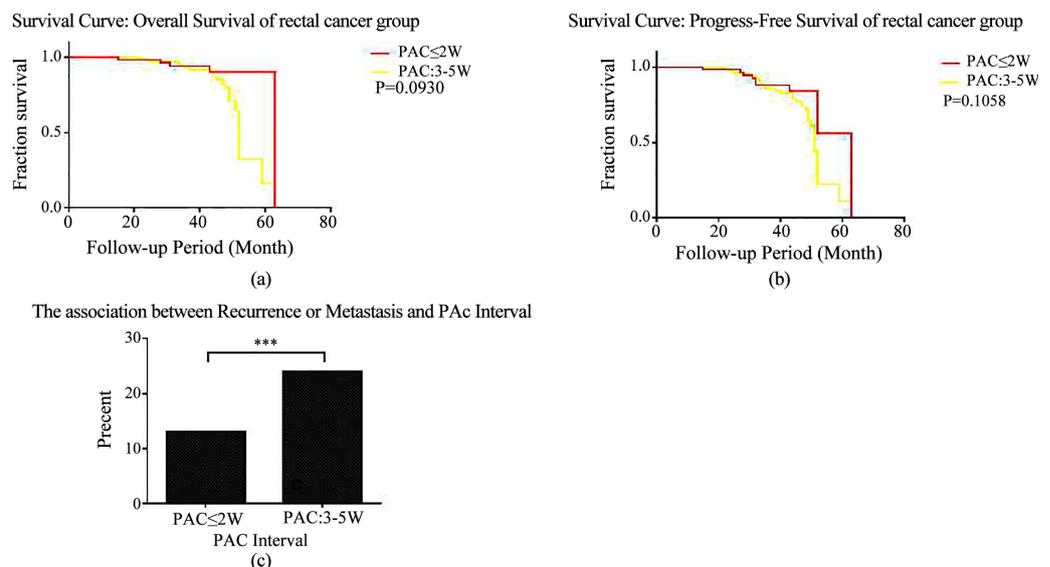
information, of whom 6 in extremely early group and 26 in normal. Hence, 235 patients were embedded in the prognostic research, 75 in extremely early group and 192 in normal group. The 3-year OS was 92.75% in case group. Compared to control group (84.34%), extremely early group patients showed a better tendency of OS, even though the differentiation was not significant ( $P = 0.0930$ ). There were also a delightful proportion of PFS in case group (86.96% vs. 75.90%), but the superiority showed no significance neither ( $P = 0.1058$ ). Interestingly, the RMR for extremely early group was significant lower than normal group (13% vs. 24%,  $P = 0.0452$ ) (**Figure 2**).

### 3.2. Quality of Life Score

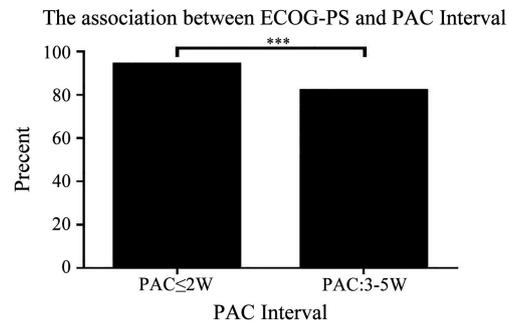
Except for those who lost to follow-up as well as death, we evaluated the quality of life for the remaining population by ECOG-PS, which presented a better life for score 0 - 1 and a worse for  $\geq 2$ . Participants had significant better quality of life from extremely early group than from control (93.65% vs. 81.56%,  $P = 0.0090$ ) (**Figure 3**).



**Figure 1.** Distribution of the different interval (in days) after surgical resection of primary tumor in two groups.



**Figure 2.** Comparison of Overall Survival (OS), Progress-Free Survival (PFS), and Recurrence and Metastasis Rate (RMR) between two groups.



**Figure 3.** ECOG-PS quality of life (0 - 1 points) according to different PAC interval in case and control group. ECOG-PS: Eastern Cooperative Oncology Group-performance status.

### 3.3. Chemotherapy-Associated Adverse Reaction

For the sake of appraising the security of extremely early to start PAC, we selectively took chemotherapy associated three major symptoms into account: chemotherapy induced nausea and vomiting (CINV), chemotherapy induced diarrhea (CTID), chemotherapy induced constipation (CIC). Those who without CTID plus CIC were defined as better defecation ability. We found there were significant lower incidences for CINV, CTID or CIC and lower degrees of chemo-associated side effects in extremely early group of PAC, which generally improved the quality of life.

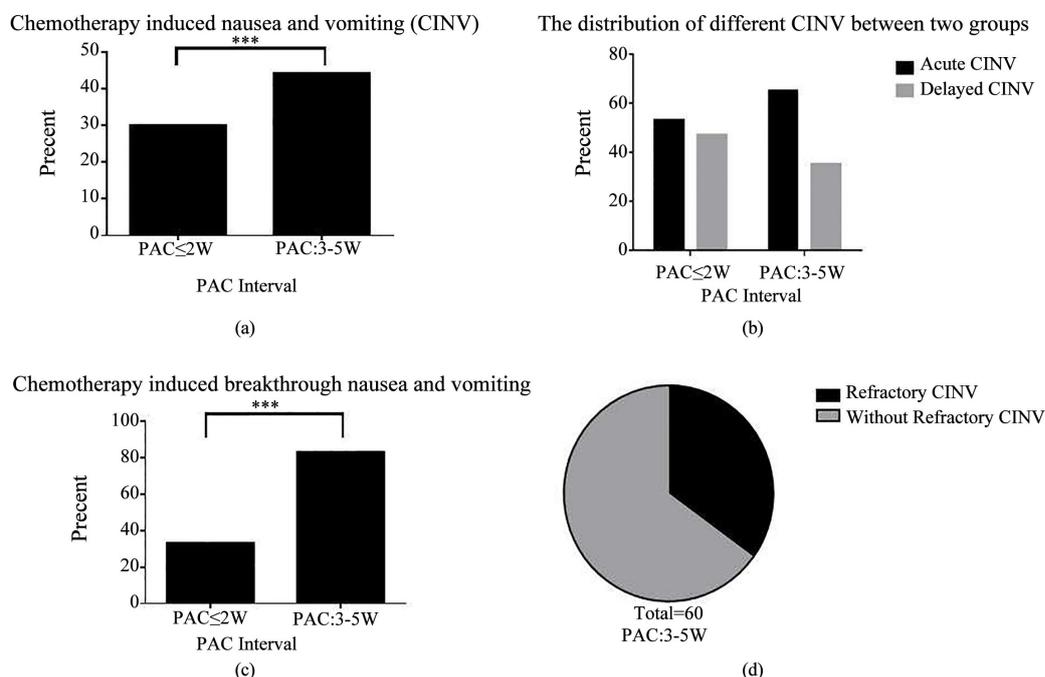
#### 3.3.1. Chemotherapy Induced Nausea and Vomiting (CINV)

First, postchemotherapy nausea and vomiting could be classified as acute CINV, delayed CINV, breakthrough CINV and refractory CINV. Acute CINV occurred within the first 24 hours, while delayed CINV occurred more than 24 hours after the chemotherapy infusion [10]. Breakthrough CINV was nausea and vomiting that occurred within 5 days after the use of guideline directed prophylactic antiemetic agents. Refractory CINV was defined as nausea and vomiting occurring after chemotherapy in subsequent chemotherapy cycles after guideline directed prophylactic antiemetic agents had failed in earlier cycles [11].

We compared various types of CINV in subgroups, which showed that the proportion of total CINV was significant lower in extremely early group (31.25% vs. 42.86%,  $P = 0.0403$ ). Furthermore, compared to 3 - 5 weeks PAC interval,  $\leq 2$  weeks had a significant cluster of less breakthrough CINV (33.30% vs. 83.30%,  $P \leq 0.0001$ ). The result also showed that acute CINV was the primary property for all patients with CINV. Interestingly, no refractory CINV happened in our case group, while there was a higher rate of 35.00% suffered from it in control (Figure 4).

#### 3.3.2. Chemotherapy Induced Diarrhea (CTID)

We found the major drugs in our hospital triggered CTID were 5-Fluorouracil and Capecitabine. The typical symptoms of this CTID included: spraying liquid stools; diarrhea with or without mild bellyache for several times to dozens of times a day. All symptoms might appear within the therapy or after.



**Figure 4.** Various types of chemotherapy induced nausea and vomiting in case and control group. CINV: Chemotherapy induced nausea and vomiting.

Three current standards were chosen to evaluate the degrees of CTID. World Health Organization (WHO) classified CTID into 4 degrees: I-IV. Eastern Cooperative Oncology Group Common Toxicity Criteria (ECOG CTC) about CTID grades: 0 - 4. National Cancer Institute Common Toxicity Criteria (NCI CTC) also defined CTID into 5 levels: 1 - 5 [12]. The higher score presented heavier response to CTID. Among the above,  $\geq 2$  or II level suggested a worse result.

On the question of CTID, this study found the proportion in shorter interval group showed statistical significant lower than the longer group (9.68% vs. 21.43%,  $P = 0.0494$ ). Another important finding was that PAC within 3 - 5 weeks suggested higher levels of CTID ( $\geq 2$  or II grade) in diverse subgroups, which demonstrated a worse chemotherapy-associated adverse reaction (Figure 5).

### 3.3.3. Chemotherapy Induced Constipation (CIC)

The National Cancer Institute graded the chemotherapy induced constipation (NIC CIC) into 5 levels: 1 - 5, and NIC CIC  $\geq 2$  suggested a severe symptom [12]. The result of this study displayed a significant decreased of CIC in case group (case vs. control: 6.35% vs. 20.00%,  $P = 0.0054$ ). 17.86% of patients in control group attached a higher grade, compared to null in case group (Figure 6).

### 3.4. Defecation Ability

Poor defecation ability was defined whom with CTID or CIC of anus or stoma after first PAC. Well defecation ability and poor defecation ability were stratified analyzed between two groups respectively. Since there were significant differ-

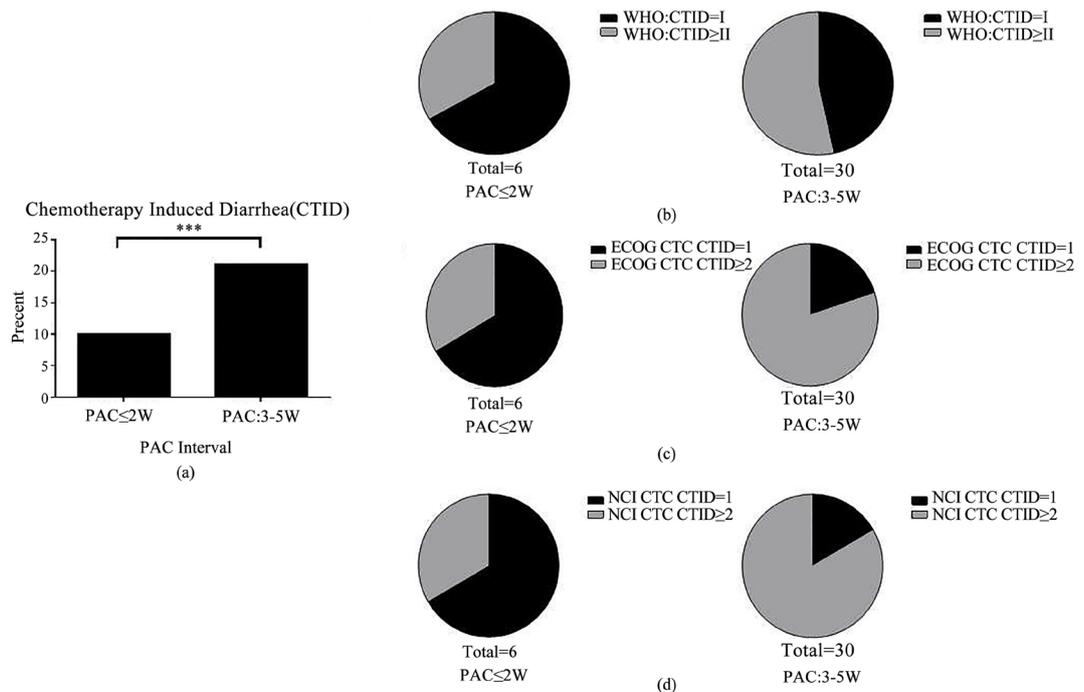
ences for these two abilities between two groups separately, obviously, when combined, a statistic worse result would achieve ( $P = 0.0149$ ), which showed a poor defecation of 20.71% happened in normal group, compared to 8.00% in extremely early group (Figure 7).

### 3.5. Postoperative Complications

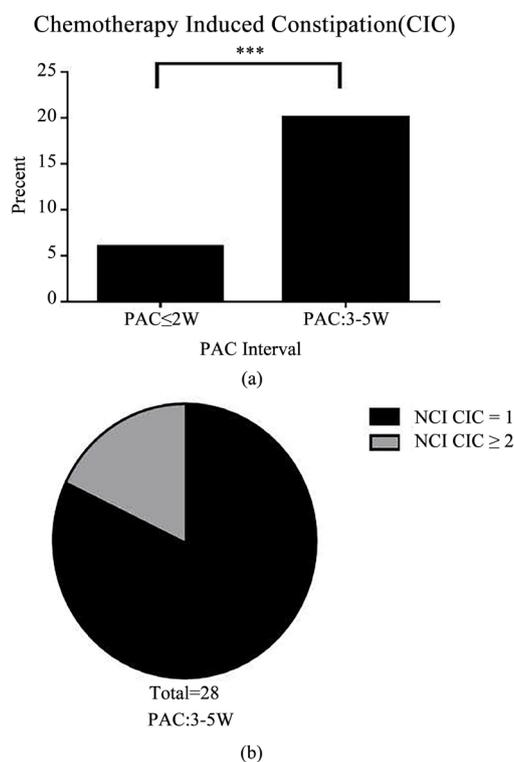
Among the whole populations, only a minority of 5.62% suffered from postoperative complications, which included reoperation, ileus, wound infection, anastomotic leak and tenesmus. Our study found a downward trend of postoperative complications in extremely PAC group, which meant early PAC would not increase the risk of postoperative complications ( $P = 0.8053$ ) (Table 2).

**Table 2.** Postoperative complications between case and control groups.

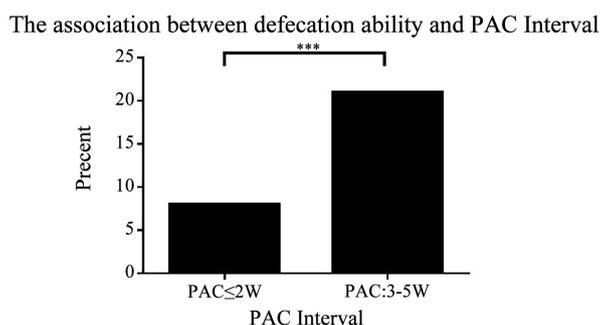
Postoperative complications	Timing of postoperative adjuvant chemotherapy		P value
	≤ 2 weeks (n = 75)	3 - 5 weeks (n =192)	
Reoperation	2	3	0.8053
Ileus	1	3	
Wound infection	0	2	
Leak	1	2	
Tenesmus	0	1	



**Figure 5.** Different classification of chemotherapy induced diarrhea between extremely early group and normal group. CTID: Chemotherapy induced diarrhea WHO:World Health Organization ECOG CTC: Eastern Cooperative Oncology Group Common Toxicity Criteria NCI CTC: National Cancer Institute Common Toxicity Criteria.



**Figure 6.** Chemotherapy induced constipation in different interval between case and control group. CIC: Chemotherapy induced Constipation NIC CIC: The National Cancer Institute grading of Chemotherapy Induced Constipation.



**Figure 7.** The association between PAC interval and defecation ability in different two groups.

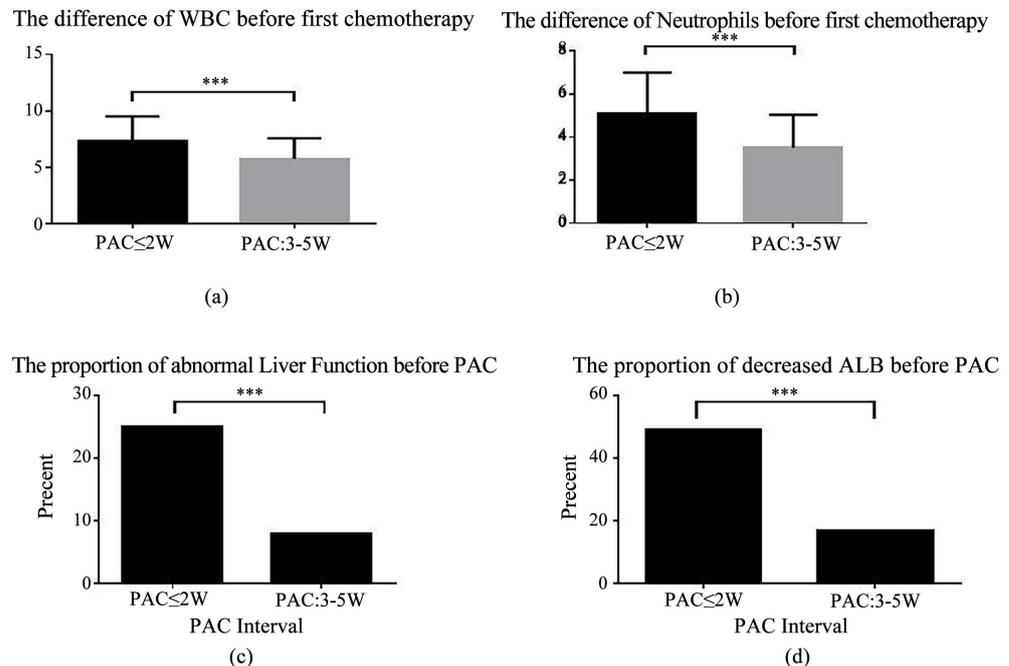
### 3.6. Variable Indexes around the First PAC

Variable factors before and after first PAC might affect the chemotherapy implementation. We performed routine blood test and liver function for regular checks around chemotherapy. Since the inflammatory factors would be elevated post-surgery, and leukopenia or liver dysfunction would appear after chemotherapy in succession, we selectively chose WBC, N, GPT, GOT and ALB for analysis.

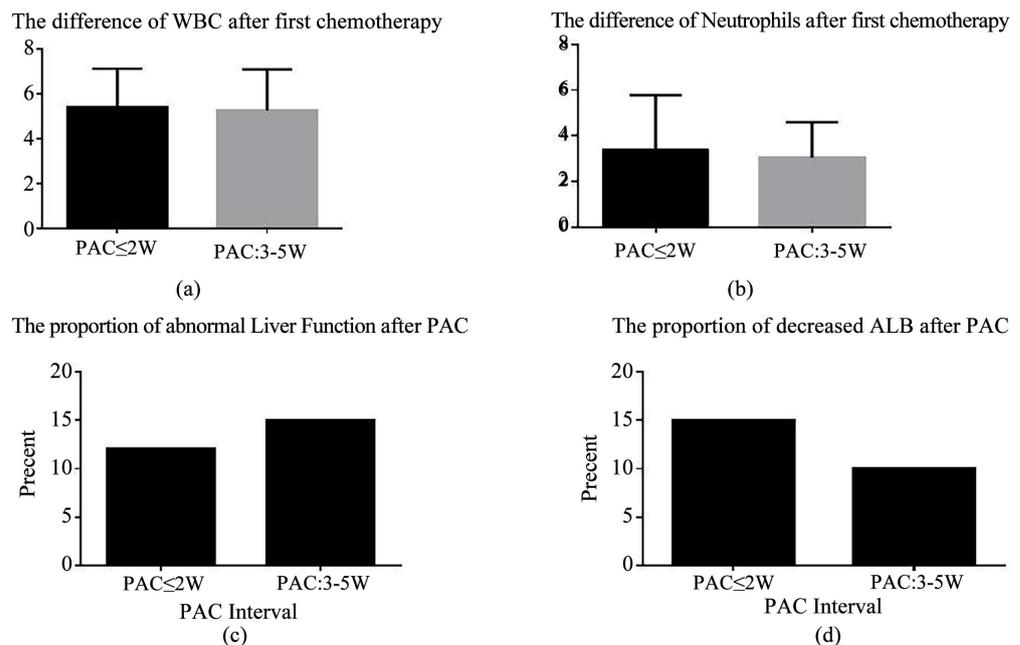
Before the first PAC, there was a significant higher level of WBC and N in extremely early group, the average values of which were  $7.322 \times 10^9/L$  and  $5.081 \times 10^9/L$  ( $P < 0.0001$ ;  $P < 0.0001$ ). Besides, GPT and GOT also significantly elevated

in the case group ( $P = 0.0020$ ), which suggested an abnormal liver function. Furthermore, the short interval might be more harmful to ALB, which had not significantly returned to a normal level ( $P < 0.0001$ ) (Figure 8).

However, after the first PAC, all above factors had no differences between two groups, since all statistical value  $P \geq 0.05$  (Figure 9).



**Figure 8.** Comparison of WBC, Neutrophils, Liver Function and ALB between case and control group before the first PAC. WBC: White Blood Cell ALB: Albumin.



**Figure 9.** Comparison of WBC, Neutrophils, Liver Function and ALB between case and control group after the first PAC. WBC: White Blood Cell ALB: Albumin.

## 4. Discussion

Available data suggested that starting the adjuvant chemotherapy earlier before 2 weeks post-surgery in stage II/III rectal cancer patients might be associated with a better OS or PFS. Extremely early initiation of PAC definitely deteriorated micrometastases and inhibited the RMR, and improved the quality of life for a long time. Throughout the whole research, population convinced less postchemotherapy adverse reactions and better defecation ability for shorter interval. After identifying factors that might influence the probability of starting PAC as well as the security of early initiation, we found that distinctive postoperative complications had not significantly changed by the PAC interval, this might attribute to a lower ratio of postoperative complications among our whole study. While, case group ought to be paid more attention to the routine blood tests with liver functions to guarantee the early implementation.

Diverse cut-offs for initiation of PAC used in previous studies lead to diverse definitions of an optimal start of chemotherapy [13]. Although current international guidelines advise the maximum interval should within 12 weeks for PAC, Chinese guidelines have advanced the deadline to an earlier date of 8 weeks [14]. Currently, many historians have argued that early start of PAC in rectal cancer patients administers an improvement of clinical prognosis. A previous study by Des Guetz G. *et al.*, [3] meta analyzed eight colorectal chemotherapy trials, showed that delaying the initiation of PAC more than 8 weeks significant decreased OS but not RFS. Similarly, Dos Santos L.V. *et al.*, [15] defined that a longer interval of either six or eight weeks before PAC would firmly reduce 5-year OS. Moreover, Sun Z. *et al.*, [16] emphasized the importance of the timely initiation, which suggested delays beyond 6 weeks were associated with a compromised survival. In addition, Alexander M. *et al.*, [6] systematic analyzed 7 articles about the initiation intervals, concluded that PAC should commence within 4 - 8 weeks for curative colorectal neoplasm patients. More recent study by Nachiappan S. *et al.*, [17] put forward that people would be benefit from initiation of PAC within 8 weeks regardless of reoperation. Furthermore, even for patients with metastatic colorectal cancer in the IV phase, several reports proposed that early initiation of PAC could significant ameliorate the prognosis after palliative operation. Two case reports conducted by Yoshida Y. *et al.*, [18] [19] in 2011 and 2012 had shown that stage IV colon cancer with liver metastases and brain metastases, after palliative resection of tumor associated metastasis, prescribing the first PAC within one week, not only the patients suffered from little chemotherapy induced adverse reactions, but the PFS had reached six months and four months, respectively. It was still Yoshida Y. *et al.*, [20] reported in 2013 that after palliative surgery for five IV stage patients with primary colorectal cancer, PAC performed on one week after operation, five patients all had no obvious adverse responses to chemotherapy, while the average PFS had reached 10.3 months.

In contrast, there are several literature holding the opposite opinions, which concludes that late initiation have no association with worse outcomes. First ar-

ticle examined by Czaykowski P.M. *et al.*, [4] summarized PAC interval  $\geq 8$  weeks wouldn't impact 5-year OS or RFS. Followed, second report by Yu S. *et al.*, [21] discovered a non-significant trend toward higher risk of recurrence when the delay of PAC more than 12 weeks compared to observation. Finally, recent research by Olsen F. *et al.*, [22] who specialized among Norwegian patients with colon cancer, found 49% of the patients didn't initiate their PAC within their 6 weeks deadline, but the related 5-year survival indicators remained at a stable level.

Based on previous researches, whether the first initiation of PAC could be carried out further in advance, just following the time after the stitches removed, is still a contradiction. Since many clinicians worry about the pharmacological and toxic effects of chemotherapeutic drugs, earlier prescribing of PAC had always failed due to the safety and complications. For example, a variety of chemotherapy agents interfere the synthesis of DNA and lead the cell damage or death, which causing the undergrowth of anastomotic stoma or anastomotic fistula. Even so, some experts take cautious attempt in extremely PAC initiation for III colorectal cancer patients. Chinese doctor Zhang Jing *et al.*, [14] defined the early interval as 3 weeks, proved early postoperative chemotherapy could effectively prolong the PFS, and decrease recurrence. Parallel reports by Liu Zhenyong *et al.*, [23] pointed out postoperative 48 hours applied with FolFox regimen had no influence on wound healing.

In our study, we believed that early start of PAC for II/III phase rectal cancer patients would bring better long-term survival as well as quality of life. The major operation methods consisted of Dixon Miles and Hartmann. Laparoscope assisted or open resection selected alternatively for all surgeries. Total participants had golden pathologically diagnosed with stage II/III post-surgery. According to different reference standards, various chemotherapy regimens were applied for populations. Since anastomotic leak always occurred in 6 - 8 days postoperative period, in order to avoid this fatal complication, we tentatively put forward 2 weeks as an extremely early interval, which the mean interval for case group was 10 days. Corresponding, to guarantee the maximum recovery from surgical strike before the first PAC, we suggested 2 weeks rest after discharging from hospital in normal group, the mean interval of which was 28 days.

There are four distinctive points that deserve to be mentioned. First, compared to previous literature, our initiation of PAC for II/III rectal cancer patient might be earlier as a whole, the longest time interval was 35 days, while the earliest was even 7 days post-surgery, albeit for Wasserman D.W. *et al.*, [24] insisted that delays in referral, consultation and chemotherapy booking would prolong the PAC interval. Meanwhile, regimes of PAC which were decided by surgeons with medical oncologists simultaneously in our hospital, might explained the low rate of late initiations in our group. The second point related to the prognostic factors, the contrast of different survival curves indicated an obvious

worse trend of morbidity and mortality in control group. The available data in our study had already successfully confirmed a lower recurrence and metastasis rate with a better quality of life for short interval to PAC. Third aspect was about the postoperative complications, several studies had revealed that complicated postoperative recovery increased the ratio of delayed PAC. [13] [25] However, no significant association between postoperative complications and PAC in our study might be due to the low incidence. The last aspect dealt with the security of early prescription. Interestingly, PAC interval  $\leq 2$  weeks not only attached less postchemotherapy side reactions, but promoted the defecation ability. The milder adverse reactions might be attributed to the consequence that chemotherapy receptors had not yet recovered to a normal sensitive level. Despite the slight symptoms brought by early PAC, the laboratory indexes put forward a higher WBC, Neutrophils, GPT, GOT with lower ALB. After all, a reasonable regulation of inflammatory factors with liver functions was a critical requirement for the successful implementation.

It should be noted that this study has limitations of a single-center and retrospective design, so selection bias and attrition bias could be inevitable. In addition, the major drawback of this approach is that the database still unable to achieve the desired goal for better OS or PFS, although a delightful trend has already sharply cleared. A larger randomized controlled trial over an extended period of time is eagerly awaited to solve this problem further. Notwithstanding its limitation, this study does suggest an appropriate analysis of the extremely early to apply adjuvant chemotherapy after surgery.

## 5. Conclusion

The first PAC could be safely applied within 2 weeks post surgery when the patient condition is available. Regular monitoring of postoperative indexes ensures the security of extremely early initiation.

## Ethics Approval and Consent to Participate

This study was approved by Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology.

## Consent for Publication

Not consent is required.

## Availability of Data and Material

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

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## Author's Contributions

LX was the only first author for this article, who contributed the conception and design of the research. LZ and YC contributed to collecting the relative follow-up data. ZH and LJ contributed to the statistical analysis. JH helped to obtain the funding. YF was the correspondence for this article, who helped in drafting and revising the manuscript. All authors gave final approval of the manuscript.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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### List of Abbreviations

PAC: Postoperative Adjuvant Chemotherapy;

OS: Overall Survival; PFS: Progress-Free Survival; RMR: Recurrence and Metastasis Rate;

ECOG-PS: Eastern Cooperative Oncology Group-performance status;

CINV: Chemotherapy induced nausea and vomiting;

CTID: Chemotherapy induced diarrhea WHO: World Health Organization;

ECOG CTC: Eastern Cooperative Oncology Group Common Toxicity Criteria;

NCI CTC: National Cancer Institute Common Toxicity Criteria;

CIC: Chemotherapy induced Constipation;

NIC CIC: The National Cancer Institute grading of Chemotherapy Induced Constipation;

WBC: White Blood Cell ALB: Albumin.