

Original Article

Efficacy and safety of perioperative chemotherapy in elderly patients with colorectal cancer

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Abstract

Aim: Chemotherapy is a common treatment for colorectal cancer, but its benefits in patients aged 75 years and older remain unclear. This study aimed to explore whether perioperative chemotherapy provided survival benefits for elderly patients with locally advanced colorectal cancer and whether elderly patients experience higher rates of chemotherapy-related toxic side effects.

Methods: In this retrospective study, 208 patients were included who were diagnosed with stage II or III colorectal cancer at the Sixth Affiliated Hospital of Sun Yat-sen University between January 2010 and December 2021, no less than 75 years old. They were divided into two groups, 40 patients in the surgery group and 168 in the perioperative chemotherapy group. Overall survival (OS) and disease-free survival (DFS) were compared as the main and secondary endpoints. The perioperative chemotherapy group was further subdivided into a neoadjuvant chemotherapy group ($n = 53$) and an adjuvant chemotherapy group ($n = 115$) to analyze the incidence of chemotherapy-related toxic side effects.

Results: At the median (range) follow-up of 24.2 (0.2-124.3) months, the perioperative chemotherapy group showed significantly prolonged OS ($P < 0.001$) and DFS ($P < 0.001$) compared with the surgery group. The same conclusion was reached when the colon and rectal cancer were discussed separately. The overall incidence of perioperative adverse events did not show significant difference among the three groups ($P = 0.059$), especially with no significant difference in grade 3-4 adverse events.

Conclusion: Perioperative chemotherapy might provide survival benefits for selectively elderly patients with locally advanced colorectal cancer without increasing severe adverse reactions, making it a potentially safe and worthwhile treatment plan.

Keywords: Colorectal cancer, perioperative chemotherapy, elderly patients

INTRODUCTION

By 2022, the global incidence of colorectal cancer (CRC) had significantly increased. Concurrently, the number of deaths escalated to 903,643, making CRC the second leading cause of cancer-related mortality worldwide^[1]. In China, by 2022, the incidence of CRC had become the second highest among malignant tumors and the mortality rate of CRC had risen to the fourth highest^[2]. Under the situation of aging population, there were increasing number of elderly patients with CRC^[3,4], with individuals over 75 years old constituting about 40% of CRC^[5,6].

Currently, the main treatments for CRC are surgery and chemotherapy^[7,8]. Stage I patients primarily undergo surgery with a favorable prognosis while stage IV patients mainly receive chemotherapy, sometimes combined with surgery, though their long-term survival rates remain poor due to the advanced nature of the disease. For stage II and III patients,

aggressive treatment can significantly prolong survival and improve quality of life. Treatment for stage II and III patients typically involves surgery combined with chemotherapy, which is effective in younger patients. However, for elderly patients, particularly those over 75, physiological degradation and increased comorbidities may make chemotherapy less tolerable and increase the likelihood of complications^[9-11]. Consequently, most clinical trials excluded this age group, resulting in a lack of evidence-based medical data for their treatment^[12,13]. Recent studies indicated that neoadjuvant perioperative chemotherapy could improve overall and progression-free survival rates compared to surgery alone by better eliminating micrometastases and reducing tumor cell shedding^[14-16]. Therefore, this study aims to explore the effectiveness and safety of perioperative chemotherapy in patients over 75 years old with CRC.

PATIENTS AND METHODS

Patients

Those enrolled in this study were consecutive patients who were treated between January 2010 and December 2021 at the Sixth Affiliated Hospital of Sun Yat-sen University for newly diagnosed CRC. Patients were included in the study who (a) were aged 75 years or older, (b) were diagnosed with clinical TNM stage II or III colorectal cancer, and (c) underwent surgical treatment. Patients were excluded from the study who (a) were younger than 75 years, (b) were diagnosed with clinical TNM stage I or IV colorectal cancer, (c) were in presence of severe underlying or concomitant diseases, or (d) had a second primary tumor. After excluding 455 patients who did not meet the inclusion criteria, the study recruited 208 patients with clinical TNM stage II or III who underwent radical excision [Figure 1]. Based on whether perioperative chemotherapy was administered, the 208 patients were divided into the surgical group ($n = 40$) and the perioperative chemotherapy group ($n = 168$). Overall survival (OS) and disease-free survival (DFS) were compared as the main and secondary endpoints. The perioperative chemotherapy group was further

subdivided into a neoadjuvant chemotherapy group ($n = 53$) and an adjuvant chemotherapy group ($n = 115$) to analyze the incidence of chemotherapy-related toxic side effects. All enrolled patients have signed an informed consent.

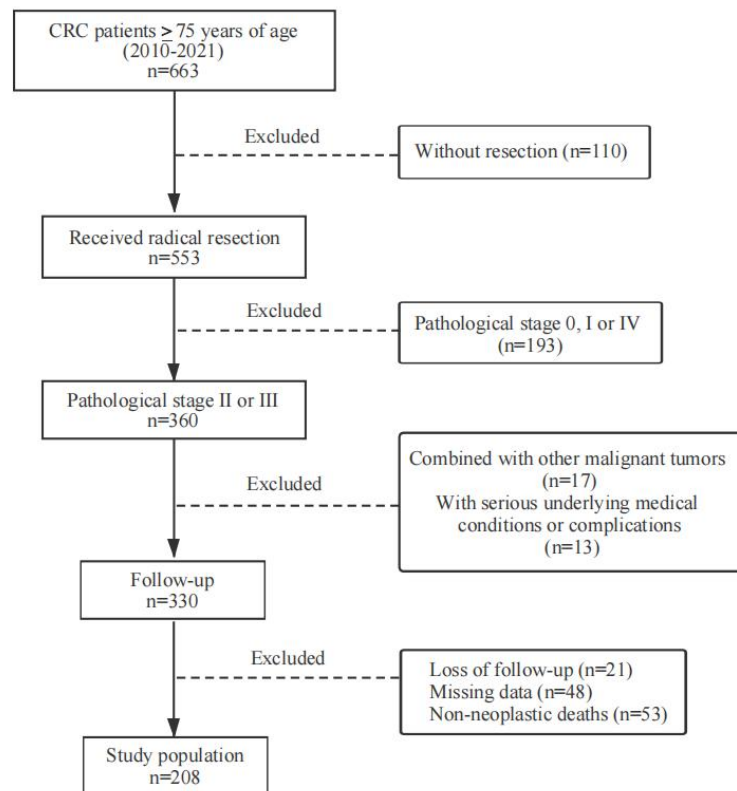


Figure 1. The CONSORT diagram. Abbreviations: CRC, colorectal cancer.

Treatment

The management chosen for each patient was determined by the attending physician and multi-disciplinary cancer team at our hospital. Perioperative chemotherapy involved a fluoropyrimidine based regimen, chosen at the discretion of the multi-disciplinary cancer team, consisting of one or more of the following: folinic acid, fluorouracil and oxaliplatin (FOLFOX); capecitabine and oxaliplatin (CAPOX); capecitabine (Xeloda); or folinic acid, fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI). The doses used were based on

recommendations from the National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology for Colon and Rectal Carcinoma. All patients provided informed consent prior to surgery. This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) methodology for retrospective cohort studies and adhered to the ethical principles outlined in the Declaration of Helsinki.

Statistical analysis

Statistical analyses were conducted using SPSS (version 26.0; SPSS Inc., Chicago, IL, USA), GraphPad Prism 8 (GraphPad Software, San Diego, California, USA), and R software version 3.5.0 for Windows (The R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org>). Statistical significance was defined as a two-sided *P* value of less than 0.05. Survival analyses, including OS and DFS were compared using the log-rank test and Kaplan-Meier method.

RESULTS

Comparison of clinicopathologic characteristics

As shown in Table 1, the median age was 77 in both the perioperative chemotherapy group and the surgery group. The male-to-female ratio was approximately 2:1 in both groups, with no significant difference ($P = 0.977$). ECOG performance status was comparable between the two groups ($P = 0.293$). All included patients had adenocarcinoma, and there was no significant difference in pathological differentiation between the groups ($P = 0.434$). In the perioperative chemotherapy group, most patients had pre-treatment stage III disease, whereas the surgery group primarily consisted of stage II patients ($P = 0.031$). Both groups were predominantly diagnosed with rectal cancer, followed by right-sided colon cancer and left-sided colon cancer ($P = 0.499$).

Table 1. Demographic and clinical characteristics of patients in the Perioperative Chemotherapy group ($n = 168$) and the Surgery group ($n = 40$).

Variables	Perioperative Chemotherapy ($n = 168$)	Surgery ($n = 40$)	<i>P</i> value
Age, median (range)	77 (75-84)	77 (75-82)	0.719§
Gender, n (%)			0.977*
Male	113 (67.3)	27 (67.5)	
Female	55 (32.7)	13 (32.5)	
ECOG score standard			0.293§
0	84 (50.0)	19 (47.5)	
1	79 (47.0)	18 (45.0)	
2	5 (3.0)	3 (7.5)	
3	0 (0)	0 (0)	
4	0 (0)	0 (0)	
Tumor location, n (%)			
Right-sided colon	42 (25.0)	13 (32.5)	
Left-sided colon	38 (22.6)	10 (25.0)	
Rectum	88 (52.4)	17 (42.5)	
Pathological type, n (%)			> 0.999 ⁺
Adenocarcinoma	168 (100)	40 (100)	
Others	0 (0)	0 (0)	
Tumor differentiation, n (%)			0.434*
Well	30 (17.9)	4 (7.5)	
Moderately	123 (73.2)	33 (82.5)	
Poorly	15 (8.9)	3 (10.0)	
Tumor size, cm, mean $\pm$	4.2 $\pm$ 1.8	3.9 $\pm$ 1.4	0.314§

SD

TNM stage, *n* (%) 0.031*

II 65 (38.7) 23 (57.5)

III 103 (61.3) 17 (42.5)

* Pearson χ^2 ; ++ Fisher's precision probability test; § Analysis of Variance.

In the perioperative chemotherapy group, the majority of patients receiving neoadjuvant chemotherapy had rectal cancer (73.6%), while colon cancer predominated (57.4%) among those receiving adjuvant chemotherapy [Table 2]. Of the 53 patients who underwent neoadjuvant chemotherapy, 28 demonstrated significant TNM stage reduction. Notably, 10 patients achieved stage I postoperatively, and 5 achieved complete remission, significantly improving their prognosis.

Table 2. Demographic and clinical characteristics of patients in the Neoadjuvant chemotherapy (*n* = 53) and Adjuvant chemotherapy group (*n*=115).

Variables	Neoadjuvant chemotherapy (<i>n</i> = 53)	Adjuvant chemotherapy (<i>n</i> = 115)	<i>P</i> value
Age, median (range)	77 (75-83)	77 (75-84)	0.369§
Gender, <i>n</i> (%)			0.901*
Male	36 (67.9)	77 (67.0)	
Female	17 (32.1)	38 (33.0)	
ECOG score standard			0.651§
0	22 (41.5)	62 (53.9)	
1	28 (52.8)	51 (44.3)	
2	3 (5.7)	2 (1.8)	
3	0 (0)	0 (0)	

4	0 (0)	0 (0)	
Tumor location, <i>n</i> (%)			0.001*
Right-sided colon	7 (13.2)	35 (30.4)	
Left-sided colon	7 (13.2)	31 (27.0)	
Rectum	39 (73.6)	49 (42.6)	
Pathological type, <i>n</i> (%)			> 0.999++
Adenocarcinoma	53 (100)	115 (100)	
Others	0 (0)	0 (0)	
Tumor differentiation, <i>n</i> (%)			0.379*
Well	8 (15.1)	22 (19.1)	
Moderately	38 (71.7)	85 (73.9)	
Poorly	7 (13.2)	8 (7.0)	
Tumor size, cm, mean $\pm$ SD	4.3 $\pm$ 1.5	4.1 $\pm$ 1.9	0.425§
TNM stage, <i>n</i> (%)			0.863*
II	20 (37.7)	45 (39.1)	
III	33 (62.3)	70 (60.9)	

* Pearson χ^2 ; ++ Fisher's precision probability test; § Analysis of Variance

Progression-free survival and overall survival

The median (range) follow-up for the cohort was 24.4 (0.3-124.3) months. In the perioperative chemotherapy group, disease-free survival (DFS) rates at 1 and 2 years were 82.3% and 64.8%, respectively, and overall survival (OS) rates were 93.5% and 78.6%, respectively. In the surgery group, DFS rates were 62.4% and 32.3%, and OS rates at 1 and 2 years were 90.0% and 48.8%, respectively. Compared to the surgery group, perioperative chemotherapy significantly improved DFS ($P < 0.001$) [Figure 2A] and OS rates ($P < 0.001$) [Figure 2B]. Due to the different responses to chemotherapy and prognoses between colon

and rectal cancer, a subgroup analysis was performed based on tumor location. The results demonstrated that perioperative chemotherapy significantly enhanced both DFS and OS rates in patients with colon and rectal cancer. For colon cancer, perioperative chemotherapy increased the 2-year DFS rate from 17.2% to 63.1% ($P < 0.001$) and OS rate from 31.5% to 76.2% ($P < 0.001$) [Figure 3A, 3B]. Likewise, in rectal cancer, perioperative chemotherapy improved the 2-year DFS rate from 51.5% to 66.5% ($P = 0.026$) and OS rate from 69.5% to 80.7% ($P = 0.028$) [Figure 3C, 3D].

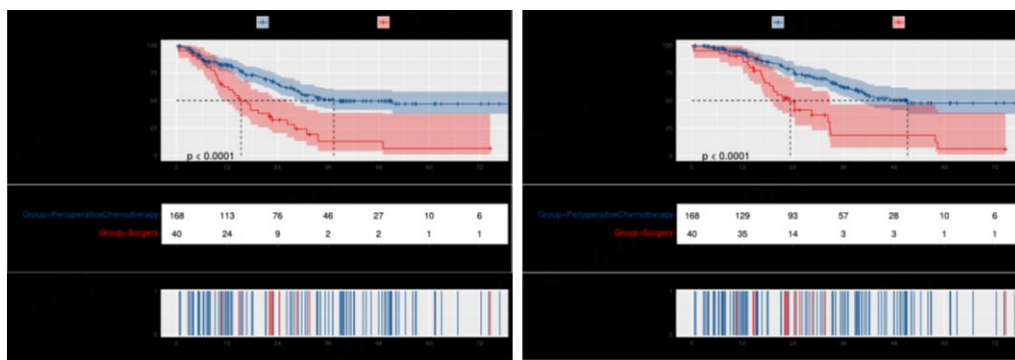


Figure 2. Kaplan-Meier curve analyses 208 patients in the perioperative chemotherapy ($n = 168$) and the surgery ($n = 40$) group. Curves show rates of (A) disease-free survival and (B) overall survival.

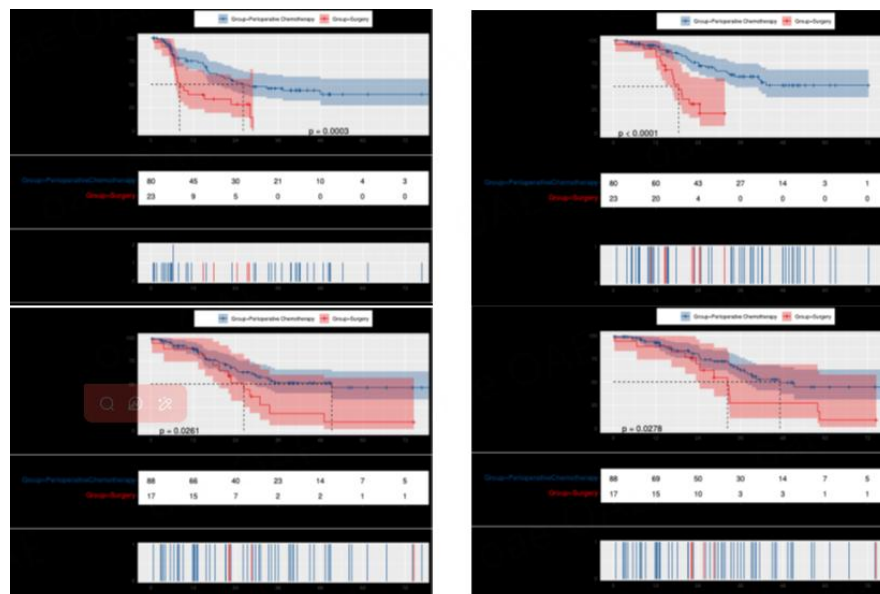


Figure 3. Kaplan-Meier analysis was performed respectively on patients with colon ($n = 103$) and rectal cancer ($n = 105$). Curves show rates of disease-free survival and overall survival of patients with colon (**A, B**) and rectal cancer (**C, D**).

Perioperative adverse reactions

The overall incidence of perioperative adverse events did not show significant difference among the three groups ($P = 0.059$), especially with no significant difference in grade 3-4 adverse events [Table 3]. Among cardiovascular grade 3-4 events, the adjuvant group experienced two cases of acute myocardial infarction and one case of ventricular tachycardia during the perioperative period. One of that myocardial infarction led to cardiac arrest and direct death of the patient, while the other patient recovered after aggressive treatment but experienced reduced cardiac function, increased surgical difficulty, and significantly decreased long-term prognosis. The neoadjuvant group experienced one case of acute congestive heart failure during the perioperative period, resulting in unsuccessful treatment and direct patient death. In hematologic grade 3-4 events, one patient in the adjuvant group developed severe granulocytopenia, leading to septic shock and subsequent death, while other patients with granulocytopenia improved after aggressive treatment. In neurological grade 3-4 events, one case of drug-induced encephalopathy occurred in both the adjuvant and neoadjuvant groups, with both patients improving after effective treatment [Table 4].

Table 3. Treatment related adverse event grading of patients in the Neoadjuvant chemotherapy ($n = 53$), the Adjuvant chemotherapy ($n = 115$) and the Surgery ($n = 40$) group.

Variables	Neoadjuvant chemotherapy ($n = 53$)	Adjuvant chemotherapy ($n = 115$)	Surgery ($n = 40$)	P value
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All adverse events				0.059 ⁺⁺
No	32 (60.4)	90 (78.3)	33 (82.5)	
Grade 1-2	17 (32.1)	20 (17.4)	7 (17.5)	
Grade 3-4	4 (7.5)	5 (4.3)	0 (0)	
Cardiac disorders				0.344*
No	46 (86.8)	105 (91.3)	34 (85.0)	
Grade 1-2	6 (11.3)	7 (6.1)	6 (15.0)	
Grade 3-4	1 (1.9)	3 (2.6)	0 (0)	
Blood and lymphatic system disorders				< 0.001 ⁺⁺
No	46 (86.8)	114 (99.1)	40 (100)	
Grade 1-2	5 (9.4)	0 (0)	0 (0)	
Grade 3-4	2 (3.8)	1 (0.9)	0 (0)	
Gastrointestinal disorders				0.511*
No	48 (90.6)	102 (88.7)	38 (95.0)	
Grade 1-2	5 (9.4)	13 (11.3)	2 (5.0)	
Grade 3-4	0 (0)	0 (0)	0 (0)	
Nervous system disorders				0.602 ⁺⁺
No	50 (94.3)	112 (97.4)	40 (100)	
Grade 1-2	2 (3.8)	2 (1.7)	0 (0)	
Grade 3-4	1 (1.9)	1 (0.9)	0 (0)	

* Pearson χ^2 ;⁺⁺ Fisher's precision probability test.

Table 4. Specific treatment related adverse events of patients in the Neoadjuvant chemotherapy ($n = 53$), the Adjuvant chemotherapy ($n = 115$) and the Surgery ($n = 40$) group.

Variables	Neoadjuvant	Adjuvant	Surgery	<i>P</i> value
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	chemotherapy (n = 53)	chemotherapy (n = 115)	(n = 40)	
Cardiac disorders				0.232 ⁺⁺
Arrhythmia	4 (7.5)	5 (4.3)	3 (7.5)	
Heart failure	1 (1.9)	3 (2.6)	3 (7.5)	
Myocardial infarction	0 (0)	2 (1.7)	0 (0)	
Chest pain - cardiac	2 (3.8)	0 (0)	1 (2.5)	
Severe agranulocytosis	7 (13.2)	1 (0.9)	0 (0)	< 0.001 ⁺⁺
Abdominal pain / Diarrhea	5 (9.4)	13 (11.3)	2 (5.0)	0.511*
Nervous system disorders				0.676 ⁺⁺
Encephalopathy	1 (1.9)	1 (0.9)	0 (0)	
Depressed level of consciousness	1 (1.9)	0 (0)	0 (0)	
Peripheral sensory neuropathy	1 (1.9)	2 (1.7)	0 (0)	

* Pearson χ^2 ; ⁺⁺ Fisher's precision probability test

DISCUSSION

Radical surgery has been widely accepted for CRC patients, as it significantly prolongs survival time even in those aged 75 years and older^[17]. However, opinions regarding whether perioperative chemotherapy provides survival benefits for elderly patients remain inconsistent. As of now, there is no large-scale clinical research targeting this population^[18]. Limited small single-center clinical trials have confirmed that elderly Stage III CRC patients benefit similarly from adjuvant chemotherapy as younger patients (18-75 years old), with no significant increase in toxicity rates^[19,20]. However, no studies have elucidated the survival benefits from neoadjuvant chemotherapy.

This study demonstrates that perioperative chemotherapy significantly prolongs OS and

DFS for elderly Stage II and III CRC patients, whether in the colon or the rectum.. Additionally, some patients in the neoadjuvant chemotherapy group experienced tumor shrinkage and downstaging, thereby securing opportunities for radical surgery for those who were initially ineligible for surgery. Furthermore, some patients achieved complete pathological response through neoadjuvant chemotherapy.

For elderly patients, physicians are most concerned about severe adverse events during chemotherapy, which may lead to treatment interruption and even endanger patient lives. In this study, perioperative chemotherapy did not increase the overall incidence of adverse events and most of these side effects were reversible reactions. It was noteworthy that severe bone marrow suppression was more prominent in the neoadjuvant chemotherapy group. This may be due to the predominant use of intravenous chemotherapy in the neoadjuvant group, while a considerable proportion of patients in the adjuvant chemotherapy group received oral chemotherapy, highlighting the mode of administration as a significant factor. Therefore, our results showed that perioperative chemotherapy is relatively safe for elderly Stage II and III CRC patients, and age should not be considered a contraindication for perioperative chemotherapy.

We are particularly concerned about grade 3 and 4 adverse events, especially those directly leading to patient death. This study recorded a total of three cases of malignant adverse events directly causing patient death, including two cardiovascular events (one in the adjuvant chemotherapy group and one in the neoadjuvant chemotherapy group) and one severe agranulocytosis (in the adjuvant chemotherapy group). Although the incidence of cardiovascular events was relatively low, they often led to serious consequences. Arrhythmias and heart failure were the most common cardiovascular events in our study. The most common arrhythmias were ventricular premature beats (2 cases in the adjuvant chemotherapy group and 3 cases in the neoadjuvant chemotherapy group), atrial premature

beats (1 case each in the adjuvant and neoadjuvant chemotherapy groups), and supraventricular tachycardia (1 case in the adjuvant chemotherapy group). Among these, one patient experienced premature ventricular contractions exceeding 10% of total heartbeats, associated with paroxysmal ventricular tachycardia. Another patient had frequent episodes of supraventricular tachycardia with accompanying hypotension during episodes, necessitating chemotherapy interruption. Both patients improved after radiofrequency ablation surgery and were able to continue subsequent chemotherapy. This suggested that perioperative chemotherapy may induce rapid arrhythmias to some extent, which were mostly mild and manageable. Four heart failure cases were reported in this study (3 cases in the adjuvant chemotherapy group and 1 case in the neoadjuvant chemotherapy group). Among these cases, two patients recovered following treatment without affecting subsequent chemotherapy. However, one patient temporarily halted chemotherapy for two cycles due to severe heart failure, subsequently resuming treatment upon improvement in cardiac function. Tragically, one patient experienced acute left heart failure and did not respond well to aggressive rescue efforts, resulting in death. These incidents underscore the presence of pre-existing chronic cardiac insufficiency or high-risk factors for cardiovascular disease, exacerbated by the potential cardiac toxicity of certain chemotherapy agents, precipitating acute heart failure. For such patients, minimizing the use of cardiotoxic drugs is recommended, alongside controlling fluid replacement rates during treatment. Continuous monitoring of pertinent indicators such as BNP, troponin levels, electrocardiography, and echocardiography is crucial. Immediate consultation with cardiovascular specialists to adjust chemotherapy regimens accordingly may mitigate the risk of heart failure. Acute myocardial infarction is a severe cardiovascular event with a poor prognosis, sometimes leading directly to patient death. This study reported one patient who died from ineffective rescue after acute myocardial infarction during chemotherapy and one patient who recovered after treatment. These cases revealed that pre-existing coronary artery stenosis that was not actively managed, coupled with hypotension during

chemotherapy, leading to acute myocardial infarction. To reduce the incidence of such malignant events, routine coronary angiography or coronary CTA should be performed to assess coronary conditions in patients with underlying coronary artery stenosis before chemotherapy. Additionally, maintaining adequate circulating blood volume and preventing hypotension during treatment may be effective methods to reduce the occurrence of such cardiovascular events.

Limitations

This study included patients with Stage II and III disease without serious underlying diseases or other malignancies, and the efficacy of perioperative chemotherapy remains uncertain for Stage IV CRC patients and those with related severe comorbidities. Moreover, this was a single-center retrospective analysis with a limited number of cases, and we look forward to further research in multicenter randomized controlled Phase III clinical trials.

CONCLUSIONS

For selectively elderly patients with locally advanced CRC, perioperative chemotherapy combined with surgery may offer disease-related survival benefits compared to surgery alone, with a manageable safety profile. Perioperative chemotherapy might be a potentially safe and worthwhile treatment plan for them.

DECLARATIONS

Authors' contributions

JH and QJY designed the study;

XL, HJY and FH performed the contouring, treatment planning, and statistical analysis;

ZML, YDZ, and XW reviewed the data; all authors discussed the data;

FYP and QJY drafted the manuscript;

and, all authors read and approved the final manuscript.

Availability of data and materials

The datasets used for this study are available from the corresponding author upon reasonable request.

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Conflict of interest

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval and consent to participate

The experimental protocol was approved by the Central Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-sen University.

Consent for publication

Not applicable.

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