Evaluation of Postoperative Chemotherapy Duration of Capecitabine-Alone Regimen for Surgery Treated Elderly Colon Cancer Patients : A Cohort Study

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Research Article

Abstract

Background: Only 50-70% elderly colon cancer patients could complete a six-month postoperative chemotherapy. It is unknown whether a shorter duration of postoperative capecitabine-alone chemotherapy would not compromise the survival. We thus conducted this study to analyze the association between postoperative chemotherapy duration of capecitabine-alone regimen and cancer specific survival (CSS) in the surgery treated elderly colon cancer patients.

Methods: We performed a retrospective cohort study in surgery treated stage III and high-risk stage II colon cancer patients aged >= 70 from two medical centers. Cox proportional hazard regression models were utilized to calculate crude and adjusted hazard ratios (HRs). The non-linear relationship between postoperative chemotherapy duration and CSS was analyzed through the restricted cubic spline regression analysis, and the threshold effect was calculated by the two-piece-wise Cox proportional hazard model.

Results: A total of 1,217 surgery treated colon cancer patients between August 1, 2013 and September 1, 2019 were reviewed and 257 stage III and high-risk stage II patients aged >= 70 were finally enrolled. Postoperative chemotherapy with capecitabine was delivered in 114 patients and 143 cases only received surgery. The capecitabine duration was generally associated with a 11% risk decrease in death (HR=0.89, 95% confidence interval (CI) 0.82 - 0.96). Non-linearity exploration suggested a threshold effect of capecitabine duration on CSS in stage III disease. The HR for death was 0.79 (95% CI: 0.68 - 0.92) with duration <= 16 (week) while 1.34 (95% CI: 0.91 – 1.97) with duration > 16 (week).

Conclusions: The postoperative capecitabine duration was significantly associated with CSS in elderly colon cancer. However, a threshold effect of capecitabine duration on survival may suggest a short-term chemotherapy could be an alternative for the conventional six-month regimen in the elderly stage III colon cancer.

Introduction

Globally, colorectal cancer (CRC) is one of the five most common causes of cancer death (1). Patients with stage III and high-risk stage II colon cancer have a risk of recurrence over 30% after surgery (2, 3). Postoperative chemotherapy has been clearly proven to decrease the recurrence risk and increase survival in patients with high-risk stage II and stage III colon cancer (4). For several decades, a six-month chemotherapy regimen has been the standard postoperative treatment in colon cancer (4, 5). However, recent studies from International Duration Evaluation of Adjuvant Therapy collaboration (IDEA) suggested noninferiority of shorter duration (3 months) of chemotherapy, as compared with 6 months, was confirmed in most colon cancer patients with CAPOX (Oxaliplatin plus capecitabine) regimen, but not in those with FOLFOX (Oxaliplatin plus 5-fluorouracil/leucovorin) regimen (6, 7). The duration effect appeared dependent on the chemotherapy regimen and it seems that the use of capecitabine could shorten postoperative chemotherapy duration without compromising survival.

So far, only a small fraction of fittest elderly was enrolled in randomized controlled trials (RCTs). Besides, the participants in the RCTs all received oxaliplatin-containing regimen, but it is still controversial to apply oxaliplatin-containing regimens for patients 70 years or older. A fluoropyrimidine alone regimen is still the recommended postoperative protocol for the elderly in clinical practice (8, 9). The limited number of elderly participants and the different recommended chemotherapy regimens for the elderly made it impossible to evaluate the effect of capecitabine duration on survival in the elderly from results of RCTs. Additionally, more than 30%-50% of patients could not complete the whole duration (10, 11). We were thus prompted to conduct this study to explore the association between the postoperative chemotherapy duration of capecitabine-alone regimen and cancer specific survival (CSS) in elderly colon cancer patients.

Materials And Methods

Study population

The data of patients was collected from the electronic medical record system from Guizhou Province Cancer Hospital and Affiliated Hospital of Guizhou Medical University. Surgery treated patients aged > or = 70, with stage III and high-risk stage II colon cancer, were included. All patients enrolled were restaged based on the 8th edition of the Union for International Cancer Control / American Joint Cancer Committee TNM staging classification. Figure 1 shows the flow chart of enrollment. The inclusion criteria for this study were as follows: 1. All patients enrolled were pathologically diagnosed as colonic adenocarcinoma; 2. They were aged > = 70 years at the time of diagnosis and underwent radical surgery; 3. They were staged as high-risk stage II (risk factors defined as tumor obstruction preoperatively, tumor perforation preoperatively, poorly differentiation, positive surgical margin, fewer than 12 lymph nodes detected, perineural infiltration, invasion of extramural venous or lymphatic vascular, or T4 disease) or stage III; 4. The enrolled patients did not receive neoadjuvant treatment.

The local ethics committee of the Guizhou Province Cancer Hospital approved this study. Informed consent from enrolled patients was not required because this was a retrospective cohort study.

Study design and variables

This retrospective cohort study aimed to assess association between postoperative capecitabine duration and CSS in elderly colon cancer patients. The postoperative capecitabine duration was described as the time between the last cycle of chemotherapy accomplished and the first cycle of chemotherapy initiated. We obtained CSS as final outcome variable. CSS was defined as the interval from diagnosis to the date of cancer-attributable mortality. The Charlson comorbidity index (CCI) has been proposed to evaluate the prognosis of CRC patients with comorbidities and frequently used in the Western countries (12–14). CCI was calculated using data regarding complications (15). We utilized clinical data from electronic medical record system to calculate CCI of each participant. Moreover, mismatch repair (MMR) status has been confirmed to be associated with response to fluoropyrimidines and recommended testing in CRC patients (16). Therefore, apart from demographic factors, CCI and clinicopathological features, we obtained MMR

status as covariates. Finally, the variables used to establish multivariable adjusted models included: (1) continuous variable: age, carcinoma antigen 199 (CA199, obtained before surgery), carcinoembryonic antigen (CEA, obtained before surgery), CCI and (2) categorical variables: gender, T stage, N stage, histological type, and MMR status.

Follow-up procedure

Follow-up for enrolled patients through the outpatient visits was applied once every three months for the first 2 years, every 6 months for the next 3 years, and every 1 year thereafter. Complete physical examination, thoraco-abdominal CT, pelvic CT, serum CEA and CA199 assessment, and annual colonoscopy were monitored at each follow-up. The last date of follow-up was September 1, 2020. Information of follow-up was achieved by the second and third authors from electronic medical record system of Guizhou Province Cancer Hospital and Affiliated Hospital of Guizhou Medical University.

Statistical analysis

Continuous variables were described as mean ± standard and categorical variables as frequency or percentage. Student's t-test (normal distribution), Mann–Whitney U test (skewed distribution), or χ^2 (categorical variables) was adopted to investigate differences of characteristics of enrolled patients among various postoperative chemotherapy duration groups. Univariate Cox proportional hazard model and multivariate Cox proportional hazard model were applied to assess variates that may correlated with risk of death. Three models were constructed: model 1, not adjusted for any covariate; model 2, adjusted for gender, age; model 3, adjusted for covariates presented in Table 1. Stratified analyses were performed by Cox proportional hazard models. Cox proportional hazards regression model with cubic spline functions and smooth curve fitting were employed to explore nonlinear relationship between postoperative chemotherapy duration and CSS. If nonlinearity was detected, then the inflection point was calculated by recursive algorithm, and a two-piecewise Cox proportional hazard model was established on both sides of the inflection point. In the end, which model was more suitable for fitting the association between target independent variable and outcome variable was mainly determined by log likelihood ratio test.

Table 1
Characteristics of enrolled patients

Characteristics	Postoperative capecitabine duration			P-value
	0	<= 12 weeks	<=24 weeks	
No. of participants	143	79	35	
Age (years), mean (SD)	77.69 (4.90)	73.57 (2.77)	73.34 (2.99),	< 0.001
>=70,<75	43 (30.07%)	46 (58.23%)	25 (71.43%)	
>=75, < 80	43 (30.07%)	33 (41.77%)	8 (22.86%)	
>=80	57 (39.86%)	0 (0.00%)	2 (5.71%)	
Gender, N (%)				0.421
Male	85 (59.44%)	54 (68.35%)	22 (62.86%)	
Female	58 (40.56%)	25 (31.65%)	13 (37.14%)	
T stage, N (%)				0.177
1−2	8 (5.59%)	2 (2.53%)	1 (2.86%)	
3	118 (82.52%)	68 (86.08%)	25 (71.43%)	
4	17 (11.89%)	9 (11.39%)	9 (25.71%)	
N stage, N (%)				0.832
0	74 (51.75%)	36 (45.57%)	18 (51.43%)	
1	57 (39.86%)	33 (41.77%)	14 (40.00%)	
2	12 (8.39%)	10 (12.66%)	3 (8.57%)	
Sage, N (%)				0.664
II	74 (51.75%)	36 (45.57%)	18 (51.43%)	
III	69 (48.25%)	43 (54.43%)	17 (48.57%)	
Histological type				0.883
Common type	122 (85.31%)	68 (86.08%)	31 (88.57%)	
Special type[a],	21 (14.69%)	11 (13.92%)	4 (11.43%)	

Notes: [a]Special type adenocarcinoma includes mucinous, signet ring cell, medullary, and undifferentiated variants.

Abbreviations: Abbreviations: CA, carcinoma antigen; CEA, carcinoembryonic antigen; MMR, mismatch repair; dMMR, mismatch repair deficiency; pMMR, proficient mismatch repair.

Characteristics	Postoperative capecitabine duration			P-value
	0	<= 12 weeks	<=24 weeks	
CA199, N (%)				0.232
Normal	122 (85.31%)	60 (76.92%)	27 (77.14%)	
Elevated	21 (14.69%)	18 (23.08%)	8 (22.86%)	
CEA, N (%)				0.830
Normal	92 (64.34%)	48 (60.76%)	23 (65.71%)	
Elevated	51 (35.66%)	31 (39.24%)	12 (34.29%)	
MMR status				0.021
dMMR	15 (10.49%)	3 (3.80%)	2 (5.71%)	
pMMR	106 (74.13%)	51 (64.56%)	28 (80.00%)	
Unknown	22 (15.38%)	25 (31.65%)	5 (14.29%)	
Charlson comorbidity index				< 0.001
<= 4	88 (61.54%)	75 (94.94%)	34 (97.14%)	
> 4	55 (38.46%)	4 (5.06%)	1 (2.86%)	

Notes: [a]Special type adenocarcinoma includes mucinous, signet ring cell, medullary, and undifferentiated variants.

Abbreviations: Abbreviations: CA, carcinoma antigen; CEA, carcinoembryonic antigen; MMR, mismatch repair; dMMR, mismatch repair deficiency; pMMR, proficient mismatch repair.

We conducted a series of sensitivity analyses to guarantee the robustness of the data analysis. Firstly, due to the limitation of the Cox proportional-hazards model in addressing non-linearity, a generalized additive model was used to adjust covariates; we then compared its effect size with a fully-adjusted model. Secondly, we used different covariates as the stratification variables to observe the trend of HR among different subgroups and calculated the P for trend. All data analysis was performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, SUA). P values < 0.05 (two-sided) was considered statistically significant.

Results

Baseline characteristics of enrolled patients

From August, 2013 to September, 2019, a total of 1,217 surgery treated colon cancer participants from Guizhou Province Cancer Hospital or Affiliated Hospital of Guizhou Medical University were retrospectively reviewed, and 257 elderly patients with stage III and high-risk stage II disease were enrolled into the final analysis. Postoperative chemotherapy with capecitabine-alone regimen was delivered in 114 (114/257, 44.36%) patients and 143 cases only received surgery. A total of 43 died of colon cancer (43/257, 16.73%) during follow-up, and 8 (8/257, 3.11%) were lost to follow-up. The median follow-up time was 30.4 months. Table 1 describes baseline characteristics of enrolled patients across categories of chemotherapy duration. No statistically significant difference was found in measures except for age, MMR status, and CCI among different chemotherapy duration groups. Compared to patients receiving postoperative chemotherapy, those who only received operation were older. Moreover, patients without postoperative chemotherapy had higher CCI and MMR deficiency (dMMR) incidents.

Association between postoperative chemotherapy duration and CSS

The results of univariate analysis were shown in Table 2. Postoperative capecitabine duration was associated with a lower death risk (hazard ratio (HR) = 0.90, 95% CI: 0.84−0.97). Patients with postoperative capecitabine < = 12 weeks or > 12 weeks were both associated with a decrease in death, compared to those treated by surgery alone (0.48, 0.24−0.99 and 0.09, 0.01−0.67 vs reference). While N2 (5.31, 2.42−11.64) vs reference), stage III (2.45, 1.26−4.78) vs stage II), and elevated CA199 (2.04, 1.04−3.98 vs normal) were associated with a higher death risk.

Table 2
Univariate analysis of enrolled patients

Variables	Mean ± SD/N (%)	Cancer specific survival
		HR (95% CI), P value
Postoperative capecitabine duration	4.65 ± 6.75	0.90 (0.84, 0.97), 0.0043
0	143 (55.64%)	1.0
<=12 weeks	79 (30.74%)	0.48 (0.24, 0.99), 0.046
<= 24 weeks	35 (13.62%)	0.09 (0.01, 0.67), 0.018
Gender		
Male	161 (62.65%)	1.0
Female	96 (37.35%)	1.12 (0.60, 2.08), 0.73
Age (years)	75.83 ± 4.60	1.06 (0.99, 1.12), 0.080
>=70, < 75	114 (44.36%)	1.0
>=75, < 80	84 (32.68%)	1.57 (0.77, 3.19), 0.21
>= 80	59 (22.96%)	1.79 (0.83, 3.87), 0.14
T stage		
1−2	11 (4.28%)	1.0
3	211 (82.10%)	1.30 (0.31, 5.44), 0.71
4	35 (13.62%)	1.13 (0.23, 5.62), 0.88
N stage		
0	128 (49.81%)	1.0
1	104 (40.47%)	1.77 (0.85, 3.67), 0.13
2	25 (9.73%)	5.31 (2.42, 11.64), < 0.0001
Stage		
II	128 (49.81%)	1.0
III	129 (50.19%)	2.45 (1.26, 4.78), 0.0083
Histological type		
Common type	221 (85.99%)	1.0
Special type	36 (14.01%)	1.69 (0.83, 3.44), 0.15
CEA		

Variables	Mean ± SD/N (%)	Cancer specific survival
		HR (95% CI), P value
Normal	163 (63.42%)	1.0
Elevated	94 (36.58%)	1.15 (0.62, 2.12), 0.66
CA199		
Normal	209 (81.64%)	1.0
Elevated	47 (18.36%)	2.04 (1.04, 3.98), 0.037
Charlson comorbidity index		
<= 4	197 (76.65%)	1.0
> 4	60 (23.35%)	1.05 (0.50, 2.19), 0.90
MMR status		
dMMR	20 (7.78%)	1.0
pMMR	185 (71.98%)	0.51 (0.21, 1.23), 0.1338
Unknown	52 (20.23%)	0.63 (0.22, 1.76), 0.3769

As reported in Table 3, three models were used to analyze the independent association of postoperative capecitabine duration on CSS. In the unadjusted model, 0.90 (HR) demonstrated that capecitabine duration was associated with a 10% decrease in risk of death (0.90, 0.84–0.97). In the adjust I model, after adjusting for gender and age, the negative relationship was still robust (0.90, 0.84–0.97). In the adjusted II model, we adjusted for gender, age, stage, CEA (elevated, normal), CA199 (elevated, normal), CCI (< = 4, > 4), histological type and MMR status as confounding factors. After adjusting for confounding factors, capecitabine duration was associated with a 11% decrease in the risk of death (0.89, 0.82–0.96). Then postoperative capecitabine duration was transformed from continuous variable to categorical variable for sensitivity analysis. The results of postoperative capecitabine duration as categorical variables were consistent with the results when capecitabine duration was a continuous variable.

Table 3
Results of multivariable analysis

	Non-adjusted[a]	Adjust I[b]	Adjust[c]
	HR (95% CI), P value	HR (95% CI), P value	HR (95% CI), P value
Postoperative capecitabine duration	0.90 (0.84, 0.97), 0.0043	0.90 (0.84, 0.97), 0.0076	0.89 (0.82, 0.96), 0.0035
0	1.0	1.0	1.0
<= 12 weeks	0.48 (0.24, 0.99), 0.046	0.46 (0.21, 0.98), 0.045	0.37 (0.17, 0.82), 0.015
<= 24 weeks	0.09 (0.01, 0.67), 0.018	0.09 (0.01, 0.69), 0.020	0.07 (0.01, 0.56), 0.012

Notes: [a]Non-adjusted model adjusted for: None

[b]Adjust I adjust for: Gender; Age.

[c]Adjust II adjust for: Gender; Age; Stage; CEA; CA199; CCI; Histological type and MMR status.

Abbreviations: HR: hazard ratio; CI: confidence interval; CA: carcinoma antigen; CEA: carcinoembryonic antigen; MMR, mismatch repair; CCI: Charlson comorbidity index.

Sensitivity analysis

For sensitivity analysis, we first set up model II which adjusted for gender, age, stage, CEA (elevated, normal), CA199 (elevated, normal), CCI (< = 4, > 4), histological type and MMR status (Table 3). The results were consistent with those of crude mode and model I. We further used different covariates as the stratification variables to observe the trend of HR among different subgroups (Fig. 2). The core results were consistent with our initial cohort. The tests for interactions were not statistically significant for age, gender, stage, histological type, CEA, CA199 or MMR status (P > 0.05).

Non-linear relationship of postoperative chemotherapy duration with CSS in stage III patients

In our study, the nonlinearity of postoperative capecitabine duration on CSS was observed in stage III (Fig. 3a, P for nonlinearity = 0.003), but not in high-risk stage II (P for nonlinearity = 0.24). After adjusting for gender, age, T stage, CA199, CEA, histological type, CCI and MMR status, smooth curve analysis and Cox proportional hazards regression model with cubic spline functions indicated that the relationship between the postoperative capecitabine duration and CSS was still non-linear and presented as L-shape in stage III elderly patients (Fig. 3b, P for nonlinearity = 0.01). Both Cox proportional hazard model and two-piecewise Cox proportional hazard model were applied to fit the association. We selected the best fit model according to P for log likelihood ratio test. Because the P for log likelihood ratio test was < 0.05, we selected the two-piecewise Cox proportional hazard model for fitting the association between

postoperative capecitabine duration and CSS in stage III elderly patients. The inflection point was calculated as 16 by using the recursive algorithm and two-piecewise Cox proportional hazard model (Table 4). The HR for the death was 0.79 (95% CI: 0.68–0.92) with postoperative capecitabine duration < = 16 (week) while 1.34 (95% CI: 0.91–1.97) with duration > 16 (week). However, in high-risk stage II patients, we didn't discover this non-linear association.

Table 4
Results of the two-piecewise linear regression model in stage III elderly patients

	HR (95% CI), P value[a]
Postoperative capecitabine duration	0.86 (0.78, 0.96), 0.0046
Inflection point of duration	
< 16	0.79 (0.68, 0.92), 0.0027
>= 16	1.34 (0.91, 1.97), 0.13
P for log likelihood ratio test	0.044
Notes: [a]Adjust for: Gender, Age, T stage, CA199, CEA, Histological type, CCI and MMR.	
Abbreviations: HR: hazard ratio; CI: confidence interval; CA: carcinoma antigen; CEA: carcinoembryonic antigen; MMR, mismatch repair; CCI: Charlson comorbidity index	

Discussion

In this retrospective cohort study, we investigated the association of postoperative chemotherapy duration of capecitabine-alone regimen to CSS for surgery treated elderly colon cancer patients. In general, the postoperative capecitabine duration was associated with a 11% decrease of death risk in the elderly, which was consistent with the findings mainly obtained from younger patients (17, 18). Further analyses in the stage III group unveiled some novel findings. Non-linearity exploration suggested that a L-shape relationship between the postoperative capecitabine duration and CSS. After adjusting potential confounding factors, the non-linear relationship between capecitabine duration and CSS was still significant (Fig. 3b, Table 4). The HR for the death was 0.79 (95% CI: 0.68–0.92) with chemotherapy duration < = 16 (week) while 1.34 (95% CI: 0.91–1.97) with duration > 16 (week).

The duration effect appeared dependent on the use of capecitabine since patients with pT4 or pN2 tumor were still recommended with 6-months FOLFOX regimen, while CAPOX duration could be shorten to 3 months regardless of high-risk factors (17). Although capecitabine-alone regimen remains to be one of the recommended postoperative protocol for the elderly, studies reported less than 50%-70% of patients could complete the whole duration. Our study found that in stage III elderly colon cancer patients, the effect of capecitabine duration on CSS changed at the turning point of duration as 16 weeks. That is, after 16-week use of capecitabine, the declining trend of death risk as increasing in chemotherapy duration disappeared. To the best of our knowledge, this study firstly demonstrated the threshold effect

of postoperative capecitabine duration on CSS in the elderly colon cancer. A short-term duration of capecitabine chemotherapy may be an alternative for the conventional six-month postoperative chemotherapy regimen in the elderly stage III colon cancer.

The threshold effect of capecitabine duration on survival which we discovered in stage III group was not detected in stage II group. The prognosis of stage II colon cancer varies greatly according to different risk factors. The 5-year survival rate of patients with stage IIB/IIC (T4) colon cancer was significantly lower than that of patients with stage IIIA (19). In addition, the prognosis of stage II patients with residual tumor was also worse than that of stage III patients, and the incidence of postoperative tumor residual in IIB/IIC stage was significantly higher than that in stage IIIA (20). Therefore, patients with certain high-risk factors in stage II may need longer capecitabine duration. A multicenter large cohort study may be needed to identify the effect of postoperative capecitabine duration on survival in terms of different high-risk factors in stage II.

Despite the International Society of Geriatric Oncology (SIOG) has recommended postoperative chemotherapy for elderly CRC patients, they tend to receive postoperative chemotherapy less frequently than non-elderly patients. In our study, 42.2% with high-risk stage II and 46.5% with stage III disease received postoperative therapy. Similarly, previous studies reported the proportion of elderly patients who received postoperative chemotherapy ranged from 15–57% (14, 21–23). These proportions were much lower than those in younger patients. Reasons for nontreatment and treatment interruptions in the elderly included comorbidities, side effects and patient choice (23). Although SIOG has recommended the performance of a comprehensive geriatric assessment (CGA) before cancer treatment (24), CGA is not frequently used in clinical practice in China. Considering the comorbidities and tolerance of side effects in the elderly may affect the postoperative chemotherapy duration and outcome, we utilized clinical data from electronic medical record system to calculate CCI and then adjusted CCI in following Cox proportional hazard models.

Our study has some strengths. To our knowledge, this is the first study to evaluate the role of postoperative capecitabine duration for the elderly patients with stage III and high-risk stage II colon cancer. We firstly reported a significant association between postoperative capecitabine duration and CSS in the surgery treated elderly colon cancer. Furthermore, a L-shape relationship between capecitabine duration and CSS in stage III elderly colon cancer was discovered, and the threshold effect of capecitabine duration on CSS in this group was found. Strict statistical adjustment was applied to minimize residual confounders in this study.

There are still some limitations included in our study. Firstly, we could not evaluate the effect of postoperative chemotherapy duration of 5-fluorouracil-alone or other regimens since the regimen applied for elderly colon cancer was capecitabine in both two medical centers. A multi-center study is needed to extract more conclusions. Secondly, bias could be caused by unmeasured confounders and residual, but the sensitivity analysis indicated that the association between postoperative chemotherapy duration and CSS was robust. Thirdly, dose reduction or significant delay was not reported. We have not found

available published data to assess the influence of dose reductions or treatment delays on survival in postoperative chemotherapy yet. Actually, a trial is ongoing to provide related knowledge (25).

Conclusions

In conclusion, the postoperative capecitabine duration was significantly associated with a decrease of death risk in elderly stage III and high-risk stage II colon cancer. However, a threshold effect of capecitabine duration on survival was found with the turning point as 16 weeks. A short-term duration of capecitabine chemotherapy may be an alternative for the conventional six-month postoperative chemotherapy regimen in the elderly stage III colon cancer.

Abbreviations

CRC
colorectal cancer
IDEA
International Duration Evaluation of Adjuvant Therapy collaboration
CAPOX
oxaliplatin plus capecitabine
FOLFOX
oxaliplatin plus 5-fluorouracil/leucovorin
RCTs
randomized controlled trials
CSS
cancer specific survival
CCI
Charlson comorbidity index
MMR
mismatch repair
CA199
carcinoma antigen 199
CEA
carcinoembryonic antigen
HR
hazard ratio
CI
confidence interval
dMMR
mismatch repair deficiency
SIOG

International Society of Geriatric Oncology
CGA
comprehensive geriatric assessment

Declarations

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guizhou Cancer Hospital (approval number: FZ 2020-4-050).

Competing interests

The authors declare that they have no competing interests

Consent for publication

Not applicable.

Authors' contributions

WWC and WLW designed the study. WWC, HMD, GW, JC and WLW involved in the postoperative management. WWC, HMD, GW, JC and WLW contributed to the collection and analysis of the study data. WWC wrote the article. HMD, GW, JC and WLW revised the manuscript. All authors read and approved the final manuscript.

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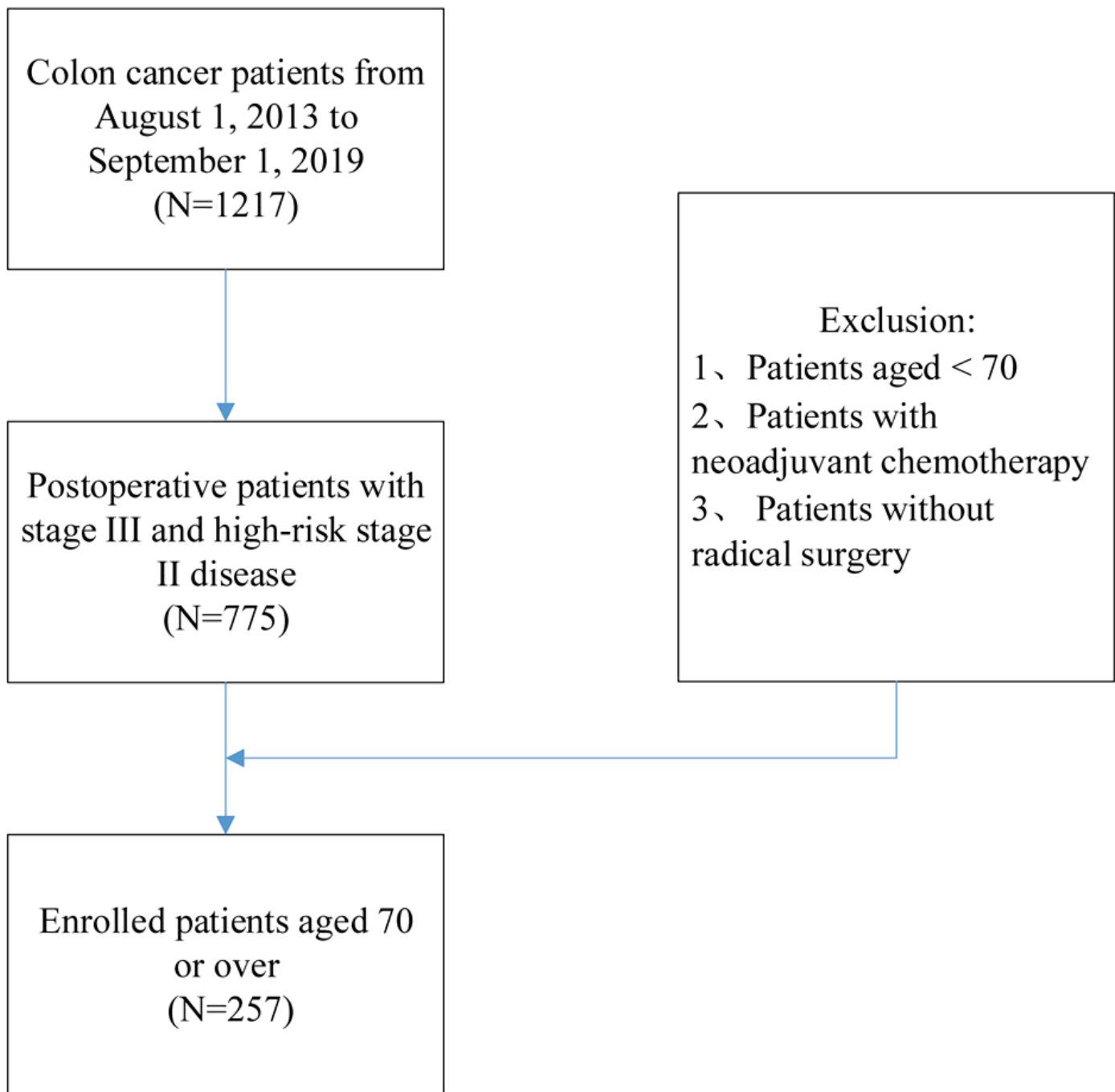
Figures

Figure 1

Flow chart of enrollment.

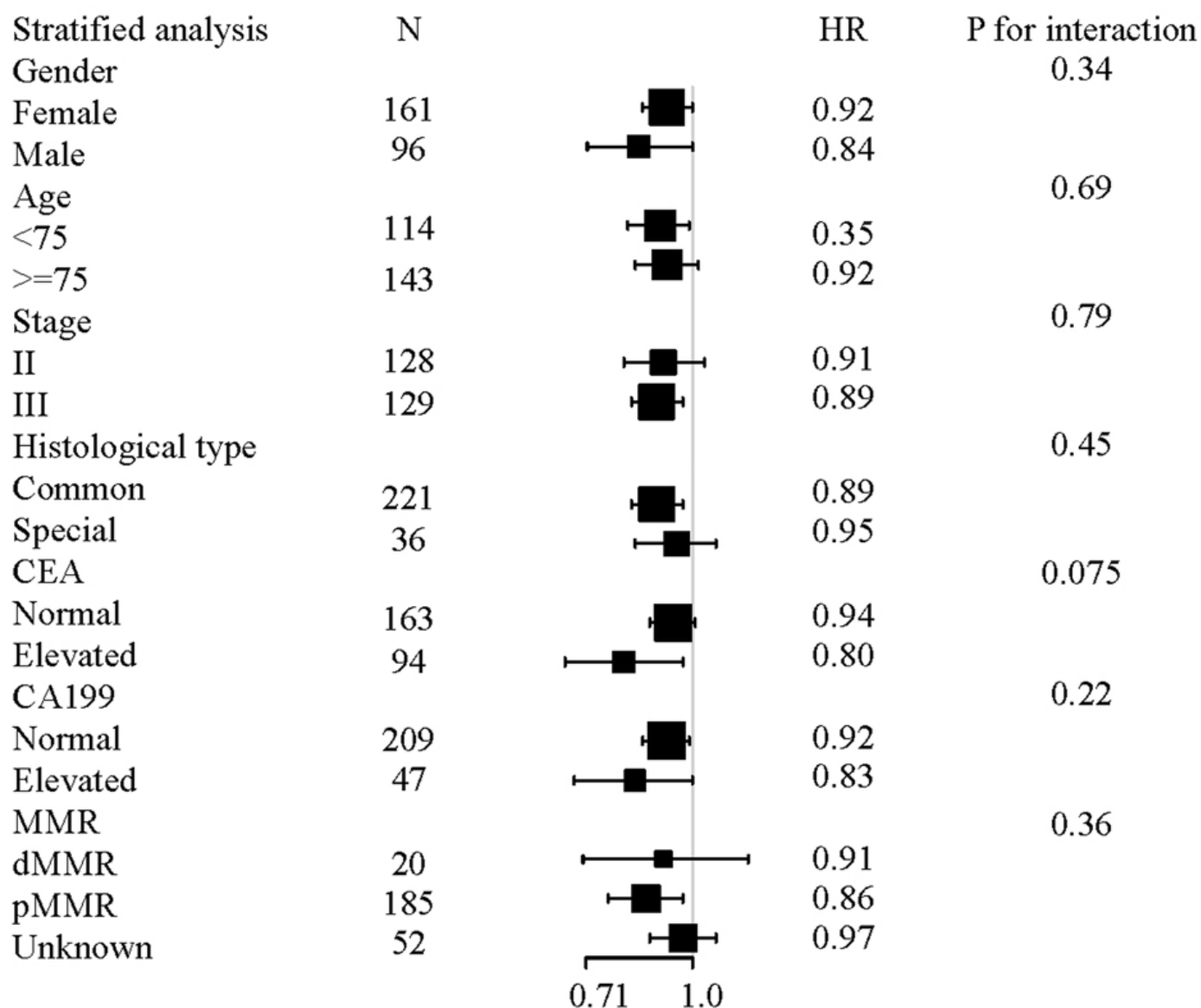| Stratified analysis	N		HR	P for interaction
Gender				0.34
Female	161		0.92	
Male	96		0.84	
Age				0.69
<75	114		0.35	
>=75	143		0.92	
Stage				0.79
II	128		0.91	
III	129		0.89	
Histological type				0.45
Common	221		0.89	
Special	36		0.95	
CEA				0.075
Normal	163		0.94	
Elevated	94		0.80	
CA199				0.22
Normal	209		0.92	
Elevated	47		0.83	
MMR				0.36
dMMR	20		0.91	
pMMR	185		0.86	
Unknown	52		0.97	

0.71   1.0

Figure 2

Subgroup analyses by gender, age, stage, histological type, CEA, CA199, MMR status in stage III and high-risk stage II colon cancer.
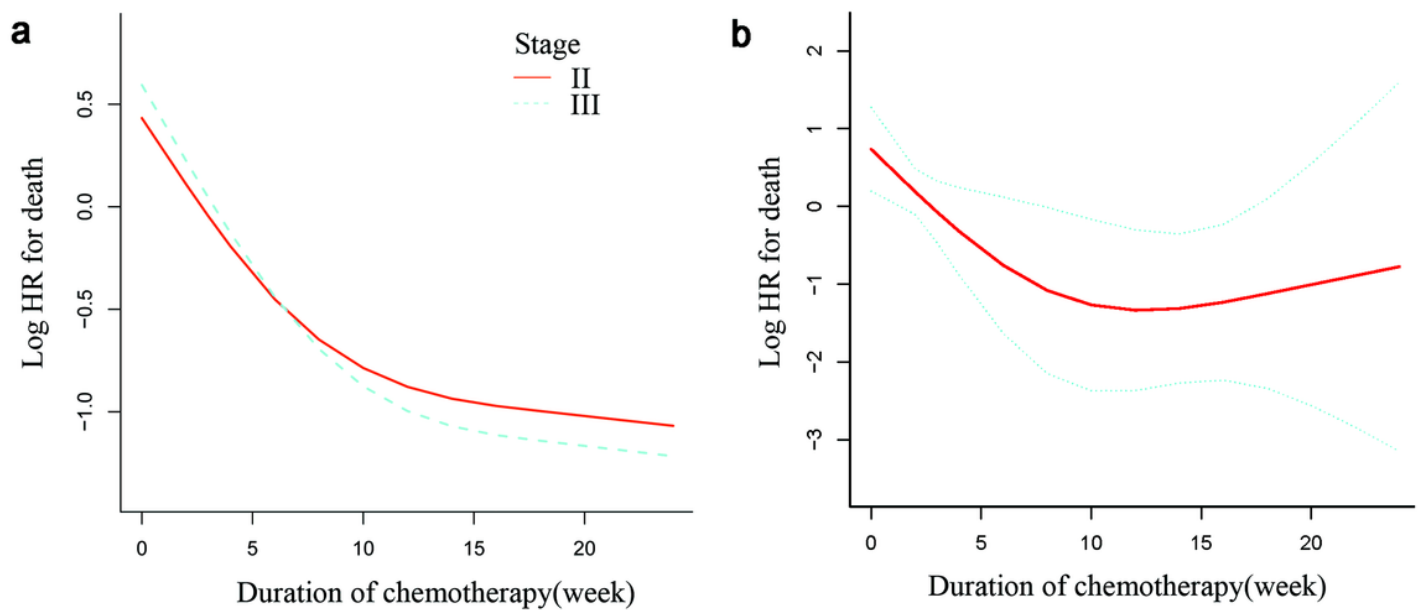
Figure 3

(A) The non-linear relationship between postoperative capecitabine duration and CSS was observed in stage III disease (P for nonlinearity = 0.003), but not in stage II disease (P for nonlinearity = 0.24). (B) The red curved line shows a L-shape relationship between the capecitabine duration and the risk of death in stage III elderly colon cancer after adjusting for gender, age, T stage, CA199, CEA, histological type, CCI and MMR status. The area between the two blue dotted lines is expressed as a 95% CI. The HR for the death was 0.79 (95% CI: 0.68 - 0.92) with postoperative capecitabine duration <= 16 (week) while 1.34 (95% CI: 0.91 − 1.97) with duration > 16 (week).