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ORIGINAL ARTICLE

Decreased survival of advanced colorectal cancer among patients with chronic cholecystitis: results from two clinical centers

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Summary

Purpose: *Chronic cholecystitis is a common inflammatory disease of the gallbladder. It is related with various gastrointestinal tumors, although its pathogenesis is not clear. This study was designed to investigate the association between chronic cholecystitis and the survival of patients with advanced colorectal cancer (CRC).*

Methods: *We conducted a population-based large-scale retrospective case-control study involving 1094 patients with advanced CRC, 286 patients with cholecystitis, and 808 without. The patients were admitted in two hospitals in China. Data were obtained from a patient survey by professional interviewers in addition to medical records. The statistical significance was estimated by Kaplan-Mayer analysis and Cox proportional hazard regression.*

Results: *The chronic cholecystitis group had a shorter survival time than non- cholecystitis group (HR for Nanfang hospital patients 0.638, 95%CI 0.457-0.890, p=0.008; HR for Changzhou No.2 hospital patients 0.583, 95%CI 0.433-0.787, p<0.001). Surgery and chemotherapy could prolong the survival of patients CRC and reduce their mortality (surgery: HR for Nanfang hospital patients 1.638, 95%CI 1.087-2.469, p=0.018; HR for Changzhou No.2 hospital patients 2.137, 95%CI 1.399-3.265, p<0.001; chemotherapy: HR for Nanfang hospital patients 1.766, 95%CI 1.238-2.518, p=0.002; HR for Changzhou No.2 hospital patients 2.616, 95%CI 1.816-3.768. p<0.001). The higher the TNM staging, the shorter the survival time (TNM staging: HR for Nanfang hospital patients 3.912, 95%CI 3.201-4.781, p<0.001; HR for Changzhou No.2 hospital patients 3.907, 95%CI 3.05-5.005, p<0.001).*

Conclusion: *Cholecystitis was strongly associated with a poor long-term prognosis for patients with CRC. The results suggest that special attention to gallbladder inflammation might be needed during the treatment of CRC.*

Key words: *colorectal cancer, chronic cholecystitis, survival time*

Introduction

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in women and the third in men [1,2]. It is a significant cause of morbidity and mortality worldwide [3]. During the last decade, CRC incidence has been rapidly increased due to the changing dietary habits, physical inactivity and sedentary lifestyle [4-6]. The overwhelming evidence indicates that chronic inflammation, diet, genetic and lifestyle factors contribute to cancer development and prognosis of CRC [4-9].

The evidence supporting a link between inflammation and the progression of cancers is growing [7,10]. Approximately 20% of all human cancers in adults result either from chronic inflammatory state or are of inflammatory etiology [10-13]. Several chronic inflammatory conditions, such as

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Crohn's disease, ulcerative colitis, chronic bronchitis and chronic pancreatitis, have been identified as important risk factors for colorectal, lung and pancreatic cancers, respectively [14].

Chronic cholecystitis is an inflammatory disease of the gallbladder, often related to cholelithiasis. Symptoms are vague and include epigastric discomfort and nausea. Recently, many microbiological studies suggest that bacterial infection in the biliary system might play a role. The presence of bacteria in the bile occurs in >25% of patients with chronic cholecystitis. Chronic cholecystitis, as a pathological state, is related to chronic inflammatory response, infection and immunization.

In the past decades, plenty of studies showed that history of cholecystectomy, cholecystitis and gallstones were associated with the tumorigenesis of the gastrointestinal track [15-18]. But in these studies, the relationship of chronic cholecystitis and the long-term survival of CRC patients was not clear. To guide decision-making for therapeutic strategies for CRC patients and improve their prognosis, a better understanding of the relevant factors affecting CRC prognosis is urgently needed. Thus, this study aimed to investigate CRC among patients with cholecystitis through a retrospective analysis, compared with patients without cholecystitis at the same time.

Ethics statement

The study protocol was approved by the institutional review board of Nanfang Hospital, Southern Medical University, Guangzhou, China (Ethical review no.157 [2012]).

Methods

Material

This study was a retrospective study. Cases were recruited through medical quality management departments between 2000 and 2014 from the medical centers Nanfang Hospital (Guangzhou, China), and Changzhou No.2 Hosptial (Changzhou, China). Excluded patients: patients who were lost due to change of address or contact phone number, who refused to be interviewed and patients with incomplete treatment information.

Demographic, clinical and tumor-related characteristics of the patients were recorded based on their hospital documents. Subjects included were patients with pathologically confirmed diagnosis of advanced colorectal adenocarcinoma, and they were admitted in two hospitals: 507 cases in Nanfang Hospital between January 01,2000 and December 31,2007; 587 cases in Changzhou No.2 Hospital from January 01,2011 to August 31,2014. Patient stage was according to TNM system of the American Joint Committee on Cancer. Patients with stage II, III and IV CRC were included in this study. In stage I cases endoscopic *en bloc* treatment can achieve a good 5-year survival and thus these patients were excluded from the study. Gallbladder diseases were diagnosed by abdominal ultrasound examination or CT scan.

The following variables were evaluated for each of the research subjects for long-term: gender, age at diagnosis, surgery, chemotherapy, survival status and survival time. The follow-up lasted at least 5 years for each patient and ended in October 30, 2012 in Nanfang Hospital, and at least 3 years in Changzhou No.2 Hospital and ended in August 31, 2014. The median follow-up time was 83.6 months and 44.43 months, respectively with a follow up success rate of 99.5%.

In Nanfang Hospital, 92.23% of those patients (463/502) were subjected to radical R_0 recession and 83.47% of them (419/502) chose FOLFOX4 as regular adjuvant chemotherapy for at least 6 cycles; 4.18% of those patients (21/502) who were unable to receive radical excision were treated with regular adjuvant chemotherapy only; 3.59% of those patients (18/502) rejected surgery and adjuvant chemotherapy and adopted palliative treatment. Survival status has been divided into alive or dead. In Changzhou No.2 Hospital, the ratio of patients who underwent surgery and received chemotherapy was 91.65% (538/587), and 44.63% (262/587), respectively. Survival time was defined as the interval between diagnosis of CRC and death resulting from any cause or follow-up cut-off time.

Statistics

Multivariate Cox regression analysis was used to analyze factors which might have an influence on the survival time: Kaplan-Meier survival analysis and log-rank test were used to compare the median survival time between cholecystitis and non-cholecystitis group, surgery and non-surgery group, chemotherapy and non-chemotherapy group. A p value of less than 0.05 was considered to indicate a statistically significant difference. Analysis was performed with the SPSS (version 13.0).

Results

General inspection of all variables in the model

The demographics of these cases are illustrated in Tables 1 and 2. There were 683 colon cancer cases and 411 rectal cancer cases in the study group which included 663 males and 431 females. Three age groups were created, including young-aged group (<45 years), middle-aged group (45-65 years) and old-aged group (> 65 years). Except that a few end-staged patients chose to give up treatment, most of the patients with CRC received comprehensive treatment including surgery, chemotherapy or other treatments.

Age and TNM staging were statistically different in the two groups (Tables 1 and 2), which may be interpreted as factors affecting the survival time. So we included the variables of the Cox proportional hazard regressions according to the value

Table 1. Patients in Nanfang Hospital (n=507)

Variables	*Cholecystitis group n (%)*	*Comparison group n (%)*	x^2	*p*
Site			0.756	0.384
Colon	64 (21.2)	238 (78.8)		
Rectum	37 (18)	168 (82)		
Gender			0.696	0.404
Male	66 (65.3)	247 (60.8)		
Female	35 (34.7)	159 (39.2)		
Age, years			7.914	0.019
<45	9 (8.9)	77 (19.0)		
45-65	45 (44.6)	188 (46.3)		
>65	47 (46.5)	141 (34.7)		
Surgery			1.128	0.288
Yes	90 (89.1)	374 (92.3)		
No	11 (10.9)	31 (7.7)		
Chemotherapy			0.024	0.876
Yes	84 (83.2)	335 (82.6)		
No	17 (16.8)	71 (17.4)		
TNM staging			10.040	0.007
TNM II	35 (34.7)	196 (48.3)		
TNM III	24 (23.8)	104 (25.6)		
TNM IV	42 (41.6)	106 (26.1)		

Table 2. Patients in Changzhou No.2 Hospital (n=587)

Variables	*Cholecystitis group n (%)*	*Comparison group n (%)*	x^2	*p*
Site			1.260	0.262
Colon	112 (60.5)	269 (78.8)		
Rectum	73 (39.5)	133 (33.1)		
Gender			0.007	0.931
Male	115 (62.2)	235 (58.5)		
Female	70 (37.5)	167 (41.5)		
Age, years			15.628	0.000
<45	5 (2.7)	28 (7.0)		
45-65	88 (47.6)	189 (47.0)		
>65	92 (49.7)	185 (46.0)		
Surgery			12.329	0.000
Yes	163 (88.1)	375 (93.3)		
No	22 (11.9)	27 (6.7)		
Chemotherapy			26.657	0.000
Yes	75 (40.5)	187 (46.5)		
No	110 (59.5)	215 (53.5)		
TNM staging			116.430	0.000
TNM II	73 (39.5)	193 (48.0)		
TNM III	74 (40.0)	158 (39.3)		
TNM IV	38 (20.5)	51 (12.7)		

of the parameters in Table 3. Maximum likelihood ratio test was used to test the statistical model. The results showed that it was statistically significant. The results showed that the omnibus tests of model coefficients had a significant difference (x^2=346.767 for Nanfang Hospital, p<0.001; x^2=314.525 for Changzhou No.2 Hospital, p<0.001, respectively). The results showed that four risk factors, including chronic cholecystitis, surgery, chemotherapy and TNM staging, affected the survival of patients with CRC (p<0.05). The survival curves are shown in Figures 1 and 2.

Table 3. The risk factors evaluated in the study

Variables	*Evaluation*
Chronic cholecystitis	with:1; without:2.
Gallbladder polyp	with:1; without:2.
Cholecystectomy	with:1; without:2.
Cholecystolithiasis	with:1; without:2.
Chemotherapy	Yes:1; No:2.
Surgery	Yes:1; No:2
TNM stage	II:2; III:3; IV:4.
Gender	Male:1; Female:2.
Survival	Survival time (months)
Age	Age (years)
Site	Colon:1; rectum:2

The influence of cholecystitis on survival of patients with colorectal cancer

The study also found that 26.14% of the patients with CRC had cholecystitis. It was shown that the 1-year, 3-year and 5-year survival rates of the cholecystitis group in Nanfang Hospital were 75.0%, 57.0%, 44.0%, and 87.3%, 71.6%, and 61.7% in the group without cholecystitis, respectively. The 1-and 3-year survival rates of the cholecystitis group in Changzhou No.2 Hospital were 78.38%, 56.76%, and 88.81%, 75.12% in the group without cholecystitis, respectively. The long history of chronic cholecystitis was a threat to long-term survival of patients with advanced CRC.

Log-rank test was used to calculate the difference between length of survival in cholecystitis and non-cholecystitis groups. The difference of survival time between the two groups was statistically significant. The median survival in the group with and without cholecystitis in Nanfang Hospital was 49.59 and 62.97 months, respectively

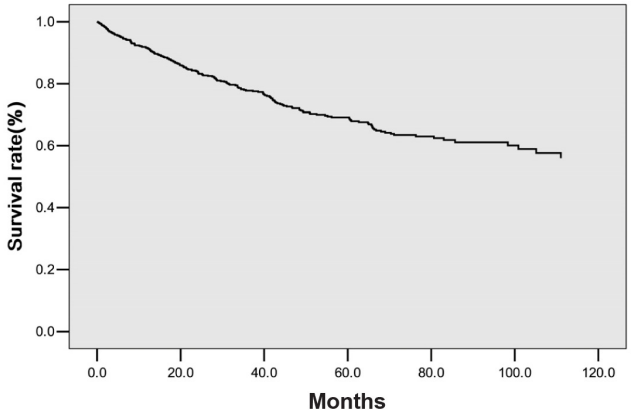

Figure 1. Survival curve for 507 colorectal cancer patients in Nanfang Hospital.

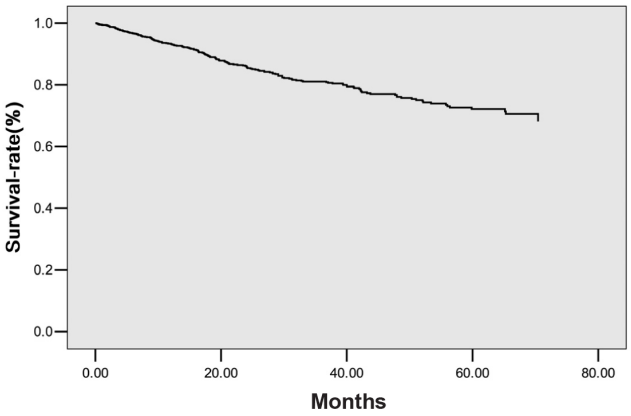

Figure 2. Survival curve for 587 colorectal cancer patients in Changzhou no.2 Hospital.

Table 4. Patients in Nanfang Hospital (n=502)

Variables	*Median survival*	x^2	*p*
Cholecystitis		27.627	<0.001
Cholecystitis group	45.033		
Non-cholecystitis group	67.400		
Surgery		84.785	<0.001
Surgery group	67.067		
Non-surgery group	9.067		
Chemotherapy		24.278	<0.001
Chemotherapy group	67.900		
Non-chemotherapy group	31.500		

(x^2=27.627, p<0.001) (Table 4), and the median survival in Changzhou No.2 Hospital was 49.59 and 62.97 months, respectively (x^2=27.627, p<0.001) (Table 5). The survival curve is shown in Figures 3 and 4. The results showed that chronic cholecystitis was a risk factor of death for patients with CRC (B=-0.450 in Nanfang Hospital, p=0.008 vs B=-0.539 in Changzhou No.2 Hospital, p<0.001, respectively), the hazard ratios for patient without chronic cholecystitis to patient with chronic cholecystitis in two hospitals were 0.638 and 0.583 (95%CI for Nanfang Hospital 0.457-0.890, p=0.008 vs 95%CI for Changzhou No.2 Hospital 0.433-0.787, p<0.008, respectively) (Tables 6 and 7).

Then, the survival rate difference between groups of different TNM stages were analyzed (Figures 5,6 and Figures 7,8). In these Figures, Kaplan-Meier method was used to confirm that CRC patients without cholecystitis had a different survival rate compared to those with cholecystitis. The results showed that stage II and III patients in the cholecystitis group had a shorter median survival than those in the non-cholecystitis group irrespective of being treated with surgery or chemotherapy. No association with tumor location was found (x^2=0.756 in Nanfang Hospital, p=0.384 and x^2=1.260 in Changzhou No.2 Hospital, p=0.262, respectively). Unexpectedly, the median survival of patients with chronic cholecystitis in stage IV patients in Nanfang Hospital was longer than the non-cholecystitis counterpart, which was opposite to other groups, perhaps because radical surgery and chemotherapy influenced greatly the physical quality of stage IV cases. Additional studies should be conducted to further confirm this.

Relationship between surgery, chemotherapy, TNM stage and survival

Consistent with many other studies, the TNM stage of CRC significantly affected patients' survival time. The higher the CRC stage, the shorter the patients' survival (HR for Nanfang Hospital 3.912, 95%CI 3.201-4.781, p<0.001; HR for Changzhou No.2 Hospital 3.907, 95%CI 3.05-5.005, p<0.001) (Tables 6 and 7). The risk of death in patients with CRC was 1.63-fold compared to those patients who were operated in Nanfang Hospital (HR 1.638,

Table 5. Patients in Changzhou no.2 Hospital (n=587)

Variables	*Number*	*Median survival-time*	x^2	*p*
Cholecystitis				
Cholecystitis group	185	39.200	20.675	<0.001
Non-cholecystitis group	402	49.750		
Surgery				
Surgery group	438	48.067	265.069	<0.001
Non-surgery group	49	6.233		
Chemotherapy				
Chemotherapy group	262	51.983	62.604	<0.001
Non-chemotherapy group	325	40.500		

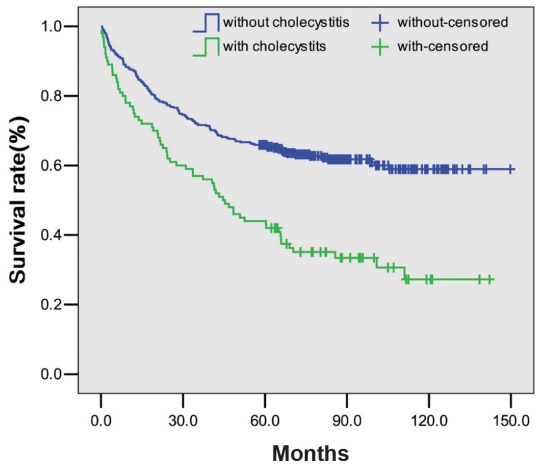

Figure 3. Survival of colorectal patients with chronic cholecystitis and a comparison group (n=502, p<0.001).

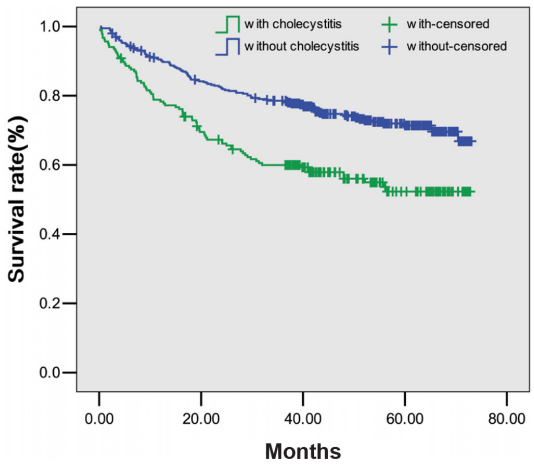

Figure 4. Survival of colorectal patients with chronic cholecystitis and a comparison group (n=587, p<0.001).

Table 6. Patients in Nanfang Hospital (n=502)[cde]

Variables	*B*	*Exp(B) (HR)*	*p value*[c]	*95%-CI for Exp(B)*
Sex	0.026	1.027	0.857	0.771-1.368
Chronic cholecystitis	-0.450	0.638	0.008	0.457-0.890
Gallbladder polyp	0.155	1.168	0.596	0.658-2.073
Cholecystectomy	0.339	1.404	0.407	0.630-3.132
Cholecystolithiasis	-0.053	0.948	0.785	0.648-1.387
Chemotherapy	0.569	1.766	0.002	1.238-2.518
Surgery	0.494	1.638	0.018	1.087-2.469
TNM stage	1.364	3.912	<0.001	3.201-4.781
Site	-0.154	0.857	0.286	0.646-1.137
Age	0.005	1.005	0.376	0.994-1.016

c: For Wald test; d: Only present variables in the equation; e: Variable selected with enter method

Table 7. Patients in Changzhou no.2 Hospital (n=587)[ce]

Variables	*B*	*Exp(B) (HR)*	*p value*[c]	*95%-CI for Exp(B)*
Sex	0.013	1.013	0.931	0.753-1.364
Chronic cholecystitis	-0.539	0.583	<0.001	0.433-0.787
Cholecystectomy	-0.069	0.933	0.823	0.509-1.71
Chemotherapy	0.962	2.616	<0.001	1.816-3.768
Surgery	0.759	2.137	<0.001	1.399-3.265
TNM stage	1.363	3.907	<0.001	3.05-5.005
Site	-0.178	0.837	0.262	0.614-1.142
Age	0.024	1.025	<0.001	1.012-1.037

c: For Wald test; e: Variable selected with enter method

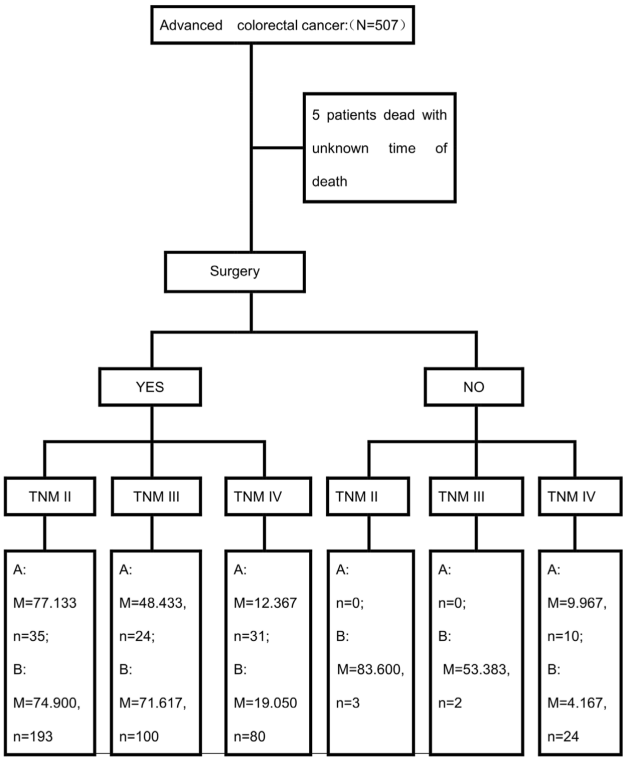

Figure 5. The impact of surgery on survival of 507 colorectal cancer patients in Nanfang Hospital.

95%CI 1.087-2.469, p=0.018), and in Changzhou No.2 Hospital, the risk was 2.137-fold (HR 2.137, 95%CI 1.399-3.265, p<0.001). The risk of death of those who did not receive chemotherapy was 1.766-fold of those who adopted chemotherapy (HR 1.766, 95%CI 1.238-2.518, p=0.002), and 2.616-fold of those in Changzhou No.2 Hospital (HR 2.616, 95%CI 1.816-3.768, p<0.001), respectively.

Log-rank test was used to calculate the difference between length of survival in the surgery group and the non-surgery group. The results suggested that the difference between the surgery and the non-surgery group was statistically significant (x^2=84.785 in Nanfang Hosptial, p<0.001; x^2=265.069 in Changzhou No.2 Hospital, p<0.001). The surgery group had a significantly longer survival (median survival: 67.067 months vs. 9.067 months in Nanfang Hospital; 48.067 months vs. 6.233 months in Changzhou No.2 Hospital). The results were also similar in chemotherapy and non-chemotherapy group (median survival: 67.900 months vs. 31.500 months; 51.983 months vs. 40.500 months in Changzhou No.2 Hospital) (x^2=24.278 in Nanfang Hosptial, p<0.001, x^2=62.604 in Changzhou No.2 Hospital, p<0.001) (Tables 4 and 5).

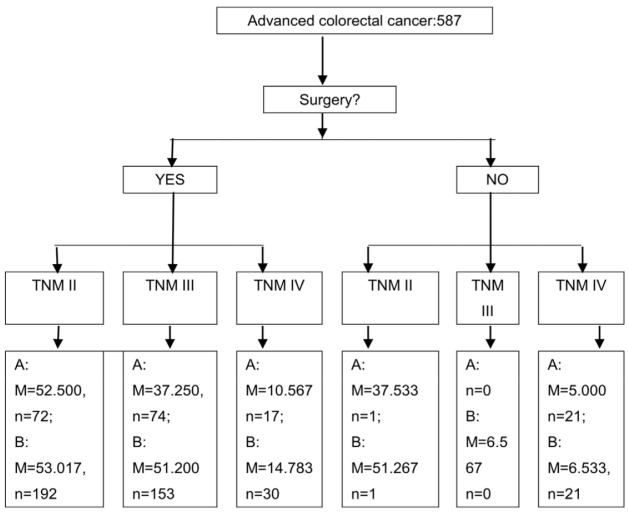

Figure 6. The impact of surgery on survival of 507 colorectal cancer patients. **A:** patients with cholecystitis; **B:** patients without cholecystitis; **M:** median survival-time (months); **n:** number.

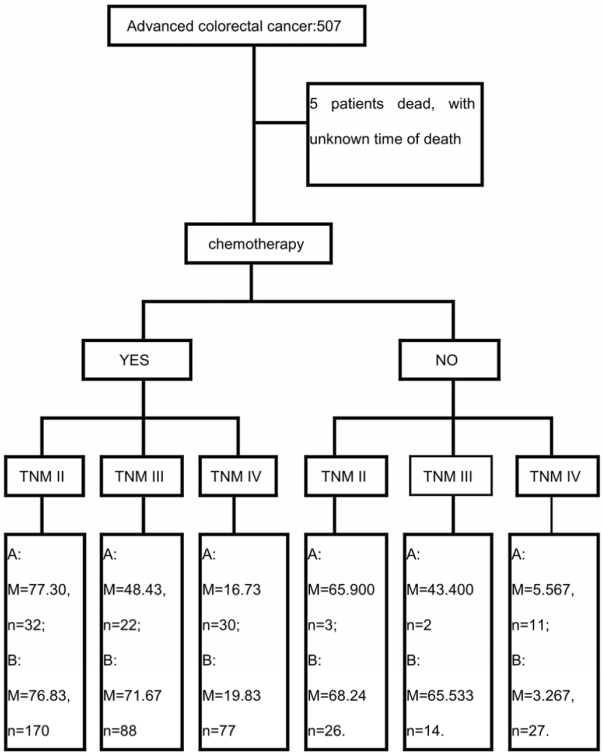

Figure 7. The impact of chemotherapy on survival of 507 colorectal cancer patients in Nanfang Hospital.

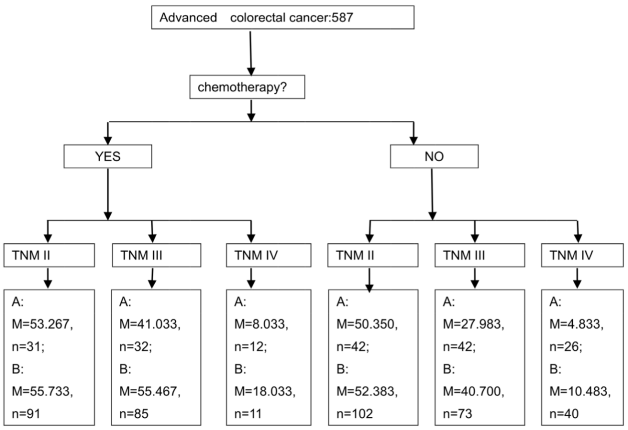

Figure 8. The impact of chemotherapy on survival of 587 colorectal cancer patients. **A:** patients with cholecystitis; **B:** patients without cholecystitis; **M:** median survival-time (months); **n:** number.

The relationship between other general clinical data and survival

At the same time, the study found that the patient age, gender, gallbladder polyp, tumor site, history of cholecystectomy and gallbladder calculus had no effect on CRC patient survival (p>0.05).

Discussion

The data from this hospital-based study indicated that CRC patients with cholecystitis had a significantly shorter survival time and a relatively lower survival rate compared to those without cholecystitis through more than 17 years follow-up. Previous studies have usually focused on the relationship between cholecystectomy or cholecystolithiasis and cancer genesis [17,19,20]. Shabanzadeh et al found that screen-detected gallstone disease in the general population was associated with pooled gastrointestinal and right-side colon cancers [19]. A study has shown that patients with biliary tract inflammation had significantly higher risk of digestive system cancers [18]. The association between chronic gallbladder inflammation and CRC has yet not been fully investigated.

Cholecystitis refers to inflammation of the gallbladder, and is most often caused because gallstone blocks fluid from passing out of the gallbladder. Infection or trauma can also cause cholecystitis. Due to ubiquitous availability and use of diagnostic ultrasound or CT scan for a wide range of abdominal complaints as well as 'routine check-ups', an increasingly frequent chronic cholecystitis is detected. Sayeed Unisa et al [21] performed a large-scaled epidemic survey in north rural India and revealed that the prevalence of gallbladder disease including cholecystitis, gallbladder stones, gallbladder carcinoma and other gallbladder diseases was 6.2%. Our research showed that 26.14% of the patients with advanced CRC had chronic cholecystitis (cases from Nanfang and Changzhou No.2 Hospital) which is much higher than the prevalence of cholecystitis in the general population, because cholecystitis occurs more frequently among cancer patients than in the general population [22].

Many studies have shown that chronic cholecystitis is a kind of inflammatory disease and has a role in tumorigenesis in the digestive tract, such as cancer of the esophagus, stomach, small intestine, liver, biliary tract, pancreas and colon/rectum [23]. This observation can be explained by the three following aspects:

Firstly, accumulated evidence has linked exposure of cells of the gastrointestinal tract to repeat high levels of bile acids as an important risk factor for gastrointestinal cancers [23-25]. High exposure to bile acids may occur in a number of settings, but most commonly is prevalent among individuals with chronic cholecystitis. Long-term high concentration of bile acid in patients with chronic cholecystitis promotes CRC [23,26]. This might be caused by stimulation of colonic epithelial cells by high concentration of bile acid, which would cause DNA damage, gene mutation, cell apoptosis and promote tumorigenesis [23-26]. Meanwhile, it was found that colorectal adenoma patients had higher serum unconjugated deoxycholic acid (DC) and isodeoxycholic acid compared with controls [23-26]. As a result, the long-term prognosis of patients with cholecystitis is worse than that of patients without.

Secondly, chronic inflammation and dysbiosis have always been recognized as prominent CRC drivers [10,11]. CRC development is initiated by indigenous bacteria with pro-carcinogenic features defined as bacterial drivers that drive epithelial DNA damage and contribute to CRC initiation. In a subsequent step, the local microenvironment is altered as a consequence of the ongoing tumorigenesis and bacterial drivers are replaced by bacterial passengers, microorganisms showing a competitive advantage in the tumor microenvironment and being capable of nurturing tumor progression [27]. The presence of bacteria in the bile occurs in > 25% of patients with chronic cholecystitis. The intestinal inflammatory microenvironment was stimulated by cholecystitis and produced highly reactive and unstable oxygen radicals, nitrogen species, cytokines, chemokines, eicanosoids, reactive aldehydes and growth factors. These might play a decisive role at different stages of tumor development, including initiation, promotion, malignant conversion, invasion and metastasis [10-13].

Thirdly, patients with cancer may have a concomitant increased risk for cholecystitis [22]. Cancer patients may develop decreased immunity and impaired infection barriers, render them generally susceptible to bacterial infections [22]. It might be attributed to the inflammatory microenvironment caused by cancer that further aggravated the poor prognosis associated with CRC.

At the same time, our research also found that there was no effect on patients survival with diseases like cholecystolithiasis, gallbladder polyps, or a history of cholecystectomy ($p>0.05$), which meant they did not increase the risk of death in patients with CRC. Though a plenty of studies have shown that cholecystolithiasis increased the risk of CRC, gallbladder resection might reduce the risk of CRC. We tend to believe it is the inflammation that increases the risk of CRC, and gallstone is a major cause of cholecystitis.

In total, gallbladder inflammation influenced the CRC formation and prognosis, and clinicians who treat cancer patients should remain vigilant about this type of infection.

Nevertheless, the findings of this study need to be interpreted with awareness of several limitations. First, the dataset used in the study lacks information on body mass index, obesity, smoking habits, alcohol use, the amount of daily fiber intake and the family economic condition. These factors are considered to be related with CRC patient prognosis. Second, because the sample size is small and insufficient, we cannot confirm that there is a definite connection between chronic cholecystitis and CRC. It still needs a much larger multicenter study to further verify the results.

In total, gallbladder inflammation influenced the CRC formation and prognosis, and clinicians who treat cancer patients should remain vigilant about this type of infection.

Conflict of interests

The authors declare no conflict of interests.

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