Original Article

Hepatitis B and/or Hepatitis C Infection does not Influence Survival Rate among Patients with Metastatic Colorectal Cancer

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Key Words
Metastatic colorectal carcinoma;
Hepatitis B;
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Chemotherapy and survival

Background. Systemic chemotherapy offers a survival advantage when treating metastatic colorectal cancer (mCRC) patients. With some cancers, patients with viral hepatitis B and/or hepatitis C infection show greater chemotherapy-related morbidity and mortality. This study investigated whether infection with hepatitis B and/or hepatitis C has an impact on the survival of mCRC patients.
Patients and Methods. The medical records of a consecutive series of 153 patients with mCRC who were treated in one institution from January 2004 to December 2007 were reviewed. Patient characteristics, hepatitis infection status, metastatic sites, and overall survival were analyzed. Those patients who underwent chemotherapy as part of their treatment regimen were analyzed separately to see if hepatitis B/C infection had any impact on survival.
Results. Multivariable Cox regression analysis of the effect of the potential impact factors on the survival of the mCRC patients showed that chemotherapy, liver metastasis, and bone metastasis were independent risk factors. Chronic hepatitis B and/or hepatitis C infection was not an independent risk factor affecting survival. The 119 mCRC patients, who received chemotherapy as part of their treatment regimen had a median survival of 623 days (95% CI, 420-825 days) among members of the no hepatitis group and 580 days (95% CI, 296-863 days) among members of the chronic hepatitis group; there was no significant overall survival difference between these two groups ($p = 0.809$).
Conclusion. In patients with metastatic colorectal cancer, chronic hepatitis B and/or C infection did not influence survival, even among patients who received chemotherapy.
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Chemotherapy is the main treatment during stage IV colorectal cancer and can have a significant impact on survival outcome.[1-3] In the Alberta Cancer Registry (Canada) data analysis, a 69% reduction in the risk of mortality was observed in patients who received chemotherapy as compared to those not receiving chemotherapy, after adjusting for age, gender, and number of metastases.[3] In a multivariate survival analysis of mCRC patients from the Eindhoven Cancer Registry (Netherlands) population-based data, it was

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found that chemotherapy use, increasing age (> 70 years old), having multiple co-morbid conditions, and having more than one tumor site significantly affected survival. The strongest effect among these factors was chemotherapy use.[1]

The fact that cancer patients with viral hepatitis B or hepatitis C infections have more chemotherapy-related morbidities and mortalities has been widely discussed.[4-12] In general, chemotherapy is considered a risk factor that may induce a viral hepatitis flare-up and may lead to hepatic failure in cancer patients.[4-13] However, in colorectal cancer, Song et al. revealed that the 5-year survival rate of their HBV infection group was 71.2%, whereas 5-year survival of the non-infection group was 55.8% ($p = 0.018$).[13] This study included all stages of colorectal cancer in which only 10% to 20% of patients had mCRC initially, and chemotherapy was not the major treatment. Focusing on the mCRC patients, whether chronic hepatitis B/C infection has an independent benefit in terms of survival is still unclear. However, no study has directly investigated this issue. In our study, we try to investigate whether hepatitis B/C infection has a survival impact on mCRC patients. We also performed a subgroup analysis among mCRC patients who had received chemotherapy to see if viral hepatitis had any survival advantage compared to non-infected patients.

Patients and Methods

Database of the Cancer Registry, Cancer Center, Chia-Yi Christian Hospital, was utilized to identify the mCRC patients. We included patients who had been pathologically diagnosed as mCRC from January 2004 to December 2007. Metastatic disease were due to previous colorectal cancer recurrence were excluded. Each patient had received a serum hepatitis B viral antigen (HBV Ag) and an anti-hepatitis C (Anti-HCV) antibody examination when they were diagnosed with cancer. All patients that were positive for HBs Ag and/or Anti-HCV were defined as having chronic hepatitis B/C infection. Patient characteristics, including gender, age, metastatic sites, treatment modalities, and survival status were collected by reviewing the medical records.

The SPSS software package (Version 15.0; SPSS, Inc., Chicago, IL) was used for statistical analysis. The Chi-squared test or Fisher's exact test was used to explore the dichotomous variables. Univariate analysis of potential prognostic factors affecting patient survival was performed by the Kaplan-Meier survival method with tests of significant differences in the survival distributions being based on the log-rank statistic. Multivariable Cox regression analysis was used to assess the independent value of any potential prognostic factors. Significant variables were retained using a likelihood ratio-based backward elimination procedure ($p \leq 0.1$). A significant difference was identified when the probability was less than 0.05.

Results

There were 153 patients with pathologically proven mCRC who were treated in Chia-Yi Christian Hospital from January 2004 to December 2007. All these patients were initially diagnosed as having stage IV disease. Among these 153 patients, 119 patients were found to be without chronic viral hepatitis, while 12 patients had chronic hepatitis B, 20 patients had chronic hepatitis C, and 2 patients had both chronic hepatitis B and chronic hepatitis C. The baseline characteristics, including gender, age, and metastatic sites, are summarized in Table 1.

The possible factors influencing survival were examined, including chronic hepatitis B/C infection, gender, age (> 70 years old or not), metastatic sites, resection of the primary tumor, radiotherapy, and chemotherapy. The results of the multivariate Cox regression analysis was followed by backward elimination of insignificant variables and a summary of the whole analysis is shown in Table 2. This shows that chemotherapy, liver metastasis, and bone metastasis were the impact factors that affected stage IV colorectal cancer survival. Hepatitis B/C infection was not an independent risk factor affecting stage IV colorectal cancer survival. Among all these 153 mCRC patients, median survival was 486 days (95% CI, 297-638 days) among those without hepatitis and 564 days (95% CI, 339-788 days) among those with chronic hepatitis B/C. This survival difference did not reach statistical

Table 1. Baseline characteristics of all mCRC patients

Overall	153
Gender	
Male (%)	87 (56.8%)
Female (%)	66 (43.2%)
Age	
< 70 yr, no. (%)	79 (51.6%)
≧ 70 yr, no. (%)	74 (48.4%)
Viral hepatitis B or C	
Yes (%)	34 (22.2%)
No (%)	119 (77.8%)
Liver metastases	
Yes (%)	96 (62.7%)
No (%)	57 (37.3%)
Lung metastases	
Yes (%)	36 (23.5%)
No (%)	117 (76.5%)
Peritoneal carcinomatosis	
Yes (%)	72 (47.1%)
No (%)	81 (52.9%)
Bone metastases	
Yes (%)	18 (11.8%)
No (%)	135 (88.2%)
Chemotherapy	
Yes (%)	119 (77.8%)
No (%)	34 (22.2%)
Radiotherapy	
Yes (%)	41 (26.8%)
No (%)	112 (73.2%)
Operation	
Yes (%)	121 (79.1%)
No (%)	32 (20.9%)

Table 2. Summary of multivariable cox regression analysis for the significant variables affecting stage IV colorectal cancer survival

Variable	Hazard Ratio	95% CI	*p*-value*
Gender			
Male	1		
Female	1.13	0.75-1.70	0.56
Age			
< 70	1		
≥ 70	1.31	0.88-1.95	0.19
Hepatitis			
No	1		
Yes	0.75	0.47-1.19	0.23
Liver metastasis			
No	1		
Yes	1.99	1.30-3.05	0.002
Bone metastasis			
No	1		
Yes	2.27	1.31-3.91	0.003
Primary tumor resection			
No	1		
Yes	0.97	0.43-2.17	0.94
Radiotherapy			
No	1		
Yes	0.71	0.43-1.15	0.16
Chemotherapy			
No	1		
Yes	0.41	0.19-0.89	0.02

Hazard Ratio (HR) was estimated using Cox proportional-hazard model.
*p-value < 0.05 is significant.

significance between the two groups ($p = 0.552$).

We next focused on the influence that chronic viral hepatitis infection had on the mCRC patients who received chemotherapy and to this end a subgroup analysis was performed. Among the 119 patients who received chemotherapy in our study, 27 patients had chronic viral hepatitis B/C while the others had neither infection. The baseline characteristics, including gender, age, and metastatic sites were similar between these two groups (Table 3). In terms of chemotherapy, the median survival was 623 days (95% CI, 420-825 days) for the no hepatitis group, and 580 days (95% CI, 296-863 days) for the chronic hepatitis group. The survival plot is shown in Fig. 1. Again there was no significant overall survival difference between the two groups ($p = 0.809$).

Discussion

Colorectal cancer is the fourth most common form of cancer occurring worldwide[14] and the most common form of cancer in Taiwan. Disease recurrence with or without visceral organ metastasis remains the common cause of mortality. Some clinical observation studies have found that colorectal cancer patients with chronic hepatitis B/C infections have a higher survival rate than those without chronic hepatitis.[13,15-18] The lower incidence of metastasis of colorectal cancer to a diseased liver, such as one with cirrhosis, is considered to contribute to this survival advantage.[13,15-20]

Table 3. Baseline characteristics of the mCRC patients receiving chemotherapy

Numbers	No hepatitis 92	Hepatitis 27*	*p*-value
Male sex, no. (%)	58 (63.0)	13 (48.2)	0.17
Age < 70 yr, no. (%)	49 (53.3)	14 (51.9)	0.90
Liver metastases, no. (%)	53 (57.6)	17 (63.0)	0.62
Lung metastases, no. (%)	25 (27.2)	6 (22.2)	0.61
Peritoneal carcinomatosis, no. (%)	47 (51.1)	10 (37.0)	0.20
Bone metastases, no. (%)	9 (9.8)	4 (14.8)	0.46
Radiotherapy, no. (%)	32 (34.8)	8 (29.6)	0.62
Operation, no. (%)	85 (92.4)	25 (92.6)	0.97

* 2 patients had chronic hepatitis B and chronic hepatitis C.

† Chi-Square test was used to compare dichotomous characteristics between hepatitis and no hepatitis.

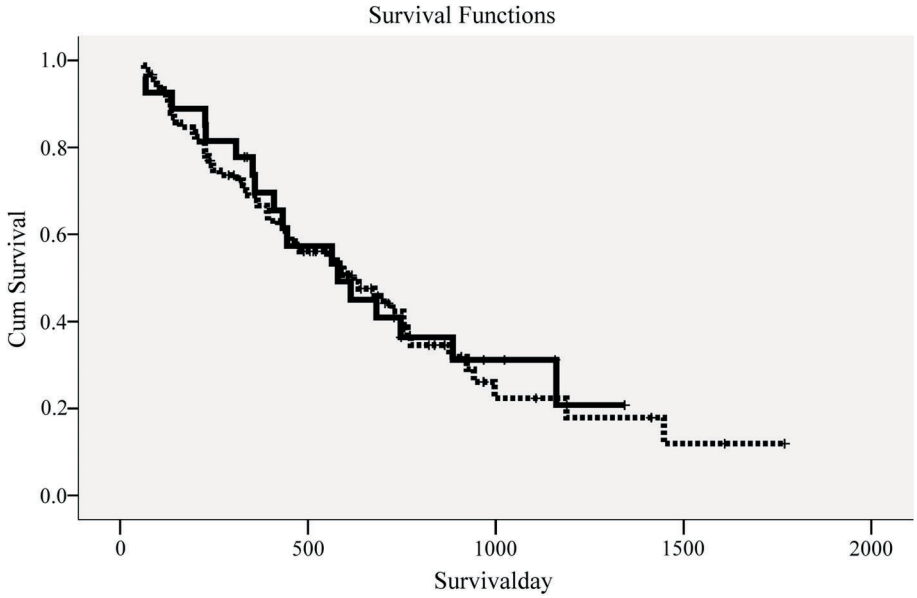

Fig. 1. Overall survival in the two groups of stage IV colorectal cancer patients who received chemotherapy. The survival of patients who did not have hepatitis is shown as a solid line and of patients who had chronic hepatitis as a dotted line ($p = 0.809$).

Chronic hepatitis B/C virus infection is well known to be among one of the most important factors that precedes liver cirrhosis. Thus, colorectal cancer patients with chronic hepatitis B/C virus infection may have a lower incidence of hepatic metastases and consequently a longer survival.[13,15-20]

The reason why cirrhotic liver has a lower rate of liver metastasis is probably due to the pathophysiological changes that occur in the endothelium of the liver sinusoids. In a normal liver, the sinusoids are lined with fenestrated endothelium and do not usually have an underlying basement membrane. In the cirrhotic liver, the endothelial fenestrations are lost and a basement membrane develops, a process called capillarization.[21] This change causes a physical barrier that may limit tumor cell invasion.[19]

It should be noted that the main treatment modalities are different for the different stages of colorectal cancer. In stage I colorectal cancer, surgery is the only major treatment. In stage II/III colon cancer, the main treatment is surgery followed by adjuvant chemotherapy. In stage II/III rectal cancer, both surgery and chemoradiation treatments offer benefits in terms of controlling the disease. Chemotherapy is the main treatment for stage IV colorectal cancer (mCRC). Therefore, the survival impact of chronic hepatitis

B/C virus infection on each stage of colorectal cancer may be different because the main treatment modalities are different at each stage.

We retrospectively analyzed the mCRC patients being treated at one institute. The possible factors influencing survival included viral infection condition, gender, age, metastatic sites, resection of the primary tumor, radiotherapy, and chemotherapy and these were all examined. Cox regression analysis showed that chemotherapy, liver metastasis, and bone metastasis were the impact factors that affected survival with mCRC. Specifically hepatitis B/C infection did not have an independent impact on mCRC survival.

In general, chemotherapy is the major treatment for mCRC and seems to offer a survival advantage to these patients. In our study, chemotherapy treatment also was showed to have survival advantage for mCRC patients. However, patients with chronic hepatitis B/C virus infection have a higher risk of developing hepatic injury, and even hepatic failure after receiving chemotherapy.[5-13] Thus, the survival impact of hepatitis B/C virus infection on mCRC patients receiving chemotherapy may be mitigated, become more ambiguous and more difficult to establish. Nevertheless, answering the question as to whether hepatitis B/C virus infection has a survival impact on mCRC patients who received chemotherapy treatment is interesting and important. However, when we did a subgroup analysis on the mCRC patients receiving chemotherapy to answer this question, the results showed there was no significant survival difference between these two groups.

One possible reason why hepatitis B/C infection did not have a survival impact on these mCRC patients receiving chemotherapy maybe the choice of chemotherapy drugs used on the mCRC patients; specifically the chosen drugs may have less chance of inducing viral reactivation. As we know, patients undergoing chemotherapy can undergo hepatitis B/C reactivation, and the severity of any morbidity will then differ depending on the chemotherapy drug used. The incidence of hepatitis B reactivation during chemotherapy is around 12% to 20% for solid tumors and 25% to 50% for lymphoma. In addition, hepatitis C reactivations have also been reported among cancer patients receiving chemotherapy or immunosuppressive treatment.[11,12] In colorectal cancer treatment, the up-front modern chemotherapy drugs of choice are oxaliplatin, irinotecan, leucovorin, and fluorouracil. Most mCRC patients are initially treated with a triple-drug combination chemotherapy (FOLFOX; FOLFIRI regimen) with or without bevacizumab or cetuximab.[1,2,22-26] Under these up-front modern chemotherapy treatments, the median survival of mCRC patient has improved substantially from 9 months (with no chemotherapy) to approximately 24 months.[2,22-26] In previous studies, up-front modern chemotherapy for mCRC may have had grade I or grade II hepatic toxicity (ranging from 7% to 54%), but very few cases have grade III or IV hepatic toxicity (ranging from 0% to 7%), when their initial liver functions were acceptable.[23-26] In our study, we also did not find any fulminate hepatitis (greater than grade III in terms of hepatic toxicity) after up-front modern chemotherapy among these mCRC patients. No patient stopped receiving chemotherapy due to hepatitis B/C-related hepatic failure, indicating that up-front modern chemotherapy drugs that are being used to treat mCRC are well tolerated by patients with chronic hepatitis B/C infection.

In summary, hepatitis B/C infection did not have an independent impact on the survival of mCRC patients. Furthermore, the survival advantage of up-front modern chemotherapy on mCRC patients was not influenced by the presence of hepatitis B/C virus infection. Chemotherapy is still the most important therapy and the survival of mCRC patients was not influenced by hepatitis B and/or hepatitis C infection.

Conclusion

In patients with metastatic colorectal cancer, having or not having chronic hepatitis B and/or hepatitis C virus infection did not influence survival, even when the patients received chemotherapy.

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原　著

B 型肝炎/C 型肝炎病毒感染不影響轉移性大腸直腸癌病患之存活

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背景　全身性化學藥物治療對轉移性大腸直腸癌病人有增加存活的好處。然而有些癌症，B 型或 C 型肝炎感染的病患接受化學藥物治療會有較多的化療相關死亡及併發症。本研究是著眼於探討轉移性大腸直腸癌病人存活率是否有受到 B 型或 C 型肝炎感染的影響。

病人及方法　針對自 2004 年一月至 2007 年十二月，在同一間醫院初診斷即為轉移性大腸直腸癌病人共 153 人進行醫療記錄的分析。病患的基本資料及相關特徵，包括病毒性肝炎感染狀況、轉移部位、存活狀況皆進行記錄及分析。也特別針對其中有接受全身性化學藥物治療的轉移性大腸直腸癌病人，B 型或 C 型肝炎感染的有無對存活率影響進行分析。

結果　經過多變項回歸分析可能影響存活率的因素後，顯示是否接受全身性化學治療、肝臟部位有轉移、骨頭部位有轉移是有意義的獨立影響因子。B 型或 C 型肝炎感染對轉移性大腸直腸癌病人的存活而言，並非為有意義的獨立影響因子。針對其中 119 位有接受全身性化學藥物治療的轉移性大腸直腸癌病人進行分析，沒有 B 型或 C 型肝炎感染的病人，存活的中位數為 623 天 (95% 信賴區間 420 至 825 天)；有 B 型或 C 型肝炎感染的病人，存活的中位數為 580 天 (95% 信賴區間 296 至 863 天)。存活率在這兩組病患並無統計上的差距 (*p* 值 0.809)。

結論　轉移性大腸直腸癌病人，慢性 B 型或 C 型肝炎感染的有無不會影響病人的存活。即使病患有接受全身性化學治療，有無 B 型或 C 型肝炎感染亦不會影響病人的存活。

關鍵詞　轉移性大腸直腸癌、B 型肝炎、C 型肝炎、化學治療、存活。