Original Article

Chronic Viral Hepatitis and Colorectal Cancer Related Liver Metastasis – A Single Institute Experience

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Key Words
Chronic hepatitis;
Hepatitis C virus;
Hepatitis B virus;
Colorectal cancer;
Liver;
Metastasis

Purpose. The rarity of the occurrence of metastatic malignancy in injured liver has been noticed. However, recent study showed that patients with liver cirrhosis related to both HBV and HCV infections have highest risk of liver metastasis. Thus, we designed this study to review the relation between HBV infection and liver metastasis of CRC.
Material and Method. A total of 565 CRC patients admitted to Chang Gung Memorial Hospital Keelung branch from January 2006 to December 2015 were recruited in this study. Patient with laboratory test of HBsAg positive and Anti-HCV positive were defined as patient with chronic hepatitis. Differences in demographic data and rate of liver metastasis between the two groups were compared by chi square test or Student t test. Overall survival (OS) and cumulative risk for liver metastasis curves were plotted with the Kaplan-Meier method, and compared by log-rank test.
Result. Liver metastasis occurred in 104 patients including synchronous liver metastasis in 82 cases and metachronous liver metastasis in 22 cases. There is no significant difference in the incidence of liver metastasis between the study group and the control group (25.9% vs. 19.4%, $p = 0.257$). There is no significant difference in the incidence of synchronous liver metastasis (18.4% vs. 16.3%, $p = 0.716$). Patients with chronic hepatitis had significantly higher risk for developing metachronous liver metastasis (11.1% vs. 4.3%, p value of log rank test = 0.044). There is no significant difference found in overall survival.
Conclusion. Chronic hepatitis infection did not have significant influence on incidence of liver metastasis in CRC patients. Patient with chronic hepatitis may have a tendency to have higher risk of developing metachronous liver metastasis. No difference were found in overall survival between the two groups.
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Colorectal cancer (CRC) is the most commonly diagnosed malignancy and is the third leading cause of cancer-related deaths in Taiwan.[1] Of these patients, about 15% have synchronous liver metastasis (LM) and 15% of the patients develop metachronous liver metastasis following treatment.[2]

Chronic HBV infection is a worldwide public health challenge. Over the past decades, it was endemic in Taiwan, where the carrier rate of hepatitis B surface antigen (HBsAg) was as high as 15-20 percent.[3] How-

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ever, after nationwide hepatitis B vaccination program, the prevalence of HBsAg had significantly decreased in young generation.[4] On the other hand, the CRC had highest prevalence in middle ages or old generation. In these age groups, chronic hepatitis B infection still had a high prevalence and need close monitoring and follow-up.

Hepatitis C virus infection is another common hepatitis in Taiwan. One study in 1999 estimated 2.3% population incidence at age between 30-64 years old. The high prevalence of HCV infection in Taiwan was due to malpractices of medical instrument or blood transfusion in early 20ths. As above background, chronic hepatitis infection related to liver injury and its relationship to colorectal liver metastasis still need further delineation.

The rarity of the occurrence of metastatic malignancy in injured liver has been noticed and described by several authors.[5-9] A review of 7 retrospective studies between 1992 and 2010 with total of 4049 patients suggest significantly lower incidence of colorectal metastasis in chronically injured liver.[10] However, a recent cohort study using nationwide population-based data in Taiwan showed that in CRC, patients with liver cirrhosis had higher risk of liver metastasis than those without liver cirrhosis. Furthermore, patients with liver cirrhosis related to both HBV and HCV infections had highest risk of liver metastasis.[11] Thus, because of the conflict of these results, we designed this study to clarify the relationship between chronic hepatitis and liver metastasis of CRC.

Materials and Method

Ethics statement

This study was reviewed and approved by the institutional review board (IRB No. 201700997B0) of Chang Gung Memorial Hospital. Informed consent was waived because the patients' personal identification numbers were de-identified.

Patients

A total of 565 CRC patients admitted to Chang Gung Memorial Hospital Keelung branch (Keelung, Taiwan) from January 2006 to December 2015 were recruited in this study. We excluded 38 patients with claims for any other malignancy, 6 lost of follow up patients after operation, and 3 patients who refused surgical treatment because of old age and bedridden state. The remaining 518 patients were enrolled in chart review and analysis (Fig. 1).

Assessment and follow-up of patients

Patients were assessed by abdominal and pelvic computed tomography (CT) scan before surgery. Patients who underwent surgery were assessed again during operation. All patients, after discharged from hospital, were followed up according to a standard protocol. The data was collected from electronic medical record including image study, outpatient department medical record, demographic data (age, gender), laboratory study (HBsAg, Anti-HCV) tumor specific feature (tumor location, size, and TNM stage), and medical record review of hepatitis infection. The diagnosis of liver metastasis was made according to CT image. Patient with laboratory test of HBsAg positive and anti-HCV positive were defined as patient with chronic hepatitis.

Statistical analysis

The statistical software SPSS (version 20.0; SPSS Inc., Chicago, IL, USA) were used for data analysis. Differences in demographic data and rate of liver metastasis between the two groups were compared by

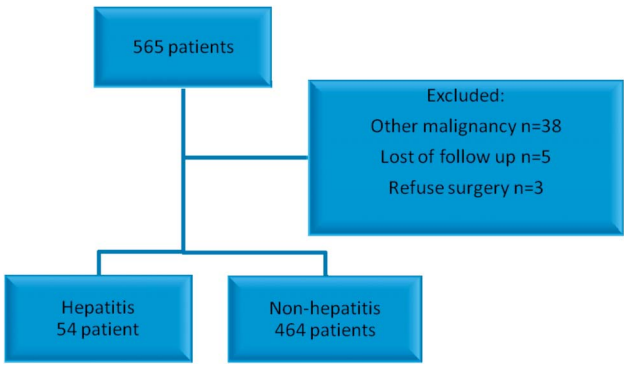

Fig. 1. Flow chart representing patient selection process.

chi-square test or Student t test. Hazard ratio (HR) and 95% confidence interval (95% CI) were calculated with the Cox proportional-hazards model. Overall survival (OS) and cumulative risk for liver metastasis curves were plotted with the Kaplan-Meier method, and compared by log-rank test. A two-tailed *p* value less than 0.05 was considered statistically significant.

Result

The 518 patients were divided into study group and control group. Fifty-five patients (10.4%) with chronic HBV infection or HCV infection were included in study group according to the presence of HBsAg or Anti-HCV. Four hundred and sixty-five patients (89.6%) were included in control group. No significant difference was found in sex, age, depth of tumor invasion, lymph-node metastasis (Table 1).

Follow-up

The mean follow-up time of patients was 36.4 months after diagnosis. The median follow-up time of patients was 29.3 months (range 0.09-116.2 months) after diagnosis.

Liver metastasis

Liver metastasis occurred in 104 patients including synchronous liver metastasis in 82 cases and metachronous liver metastasis in 22 cases. There is no significant difference in the incidence of liver metastasis between the study group and the control group (25.9% vs. 19.4%, $p = 0.257$) (Table 2). There is also no significant difference in the incidence of synchronous liver metastasis (18.4% vs. 16.3%, $p = 0.716$) (Table 3). The incidence of metachronous liver metastasis was close to statistically significantly higher in study group than control group (11.1% vs. 4.3%, $p = 0.050$) (Table 4).

Survival analysis

For stage I-III patients, patients with chronic hepatitis had significant higher risk for developing metachronous liver metastasis (11.1% vs. 4.7%, *p* value of log rank test = 0.044) (Fig. 2). There is no significant

Table 1. Baseline characteristics of patients

	Study group	Control group	*p* value
Sex			0.387
Female	28 (51.9%)	209 (44.9%)	
Male	26 (48.1%)	256 (55.1%)	
Age			0.991
Median	66.69	66.67	
Depth of tumor invasion			0.257
T1	8 (15.4%)	48 (11.1%)	
T2	4 (7.7%)	47 (10.8%)	
T3	35 (67.3%)	256 (59.0%)	
T4	5 (9.6%)	83 (19.1%)	
Lymph-node metastasis			0.583
N0	22 (42.3%)	210 (48.4%)	
N1	19 (36.5%)	129 (29.7%)	
N2	11 (21.2%)	95 (21.9%)	

Table 2. Liver metastasis (synchronous + metachronous) in tow groups

	Study group	Control group	*p* value	Odds ratio
Liver metastasis			0.257	1.454 (95% CI 0.759~2.788)
Yes	14 (25.9%)	90 (19.4%)		
No	40 (74.1%)	374 (80.6%)		

Table 3. Synchronous liver metastasis in two groups

	Study group	Control group	*p* value	Odds ratio
Synchronous liver metastasis			0.716	1.153 (95% CI 0.536~2.478)
Yes	9 (18.4%)	73 (16.3%)		
No	40 (81.6%)	374 (83.7%)		

Table 4. Metachronous liver metastasis in two groups

	Study group	Control group	*p* value	Odds ratio
Metachronous liver metastasis			0.050	2.750 (95% CI 0.963~7.851)
Yes	5 (11.1%)	17 (4.3%)		
No	40 (88.9%)	374 (95.7%)		

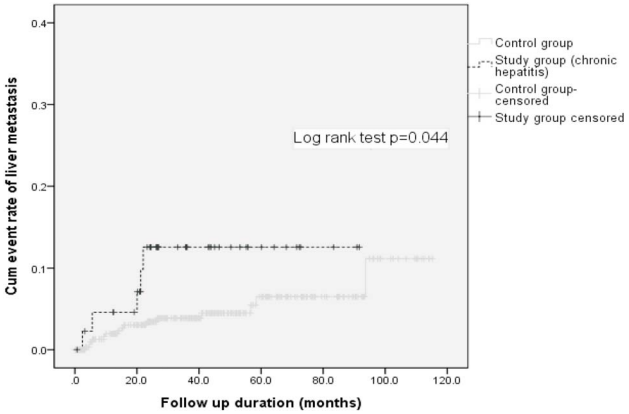

Fig. 2. Liver metastasis rate after diagnosis.

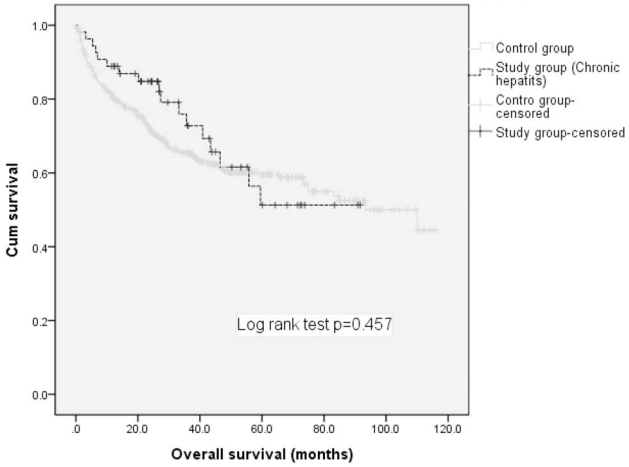

Fig. 3. Overall survival after diagnosis.

difference in overall survival between the two groups (Fig. 3).

Discussion

The rarity of the occurrence of metastatic malignancy in injured liver has been noticed and described in different malignancies.[5-9,12] However, recent nationwide population-based cohort study in Taiwan seems not to be in accordance with previous studies.[11] In our study, there was no significant relationship between liver metastasis rate and chronic hepatitis. Patient with chronic hepatitis may have shorter liver-metastasis free interval and increased cumulative incidence of liver metastasis in metachronuos group. In overall survival, there was no difference between patients with hepatitis and without hepatitis, which is consistent with previous studies.[13,14]

The mechanism how hepatitis infection affects CRC cell colonization in liver remains unclear. Earlier study suggested that the diseased liver is not a favorable soil for metastatic tumor cells seeding which formed the bad soil hypothesis.[6] This hypothesis had been further ascertained in the following observational studies.[5-9,12] However, no fundamental mechanism been approved. It was thought that host immune or para-immune defenses plays a role.[15] It has been reported that during chronic hepatitis, T cell-mediated cytotoxic pathway and a putative role for Kuppfer cells via lytic protein release was activated.[16] This was thought to be one of the reasons why chronic hepatitis protects liver from metastases. However, other conflicting conjecture was proposed. One study showed that the induction of Myeloid-derived suppressor cells (MDSCs) by HCV infection suppresses NK cell responses in liver[17] which promote the colonization of CRC cells to formed metastasis foci.. From above speculations, the complex immune responses induced by hepatitis virus infection could promote and inhibit CRC liver metastasis.

Because of the different immune effects of different hepatitis, we did subgroup analysis and showed a non-significant higher liver metastasis rate in chronic hepatitis C than in chronic hepatitis B (Fig. 4). Most of the previous studies which showed protective effect of hepatitis on CRC liver metastasis are related to hepatitis B. We speculate that hepatitis B and hepatitis C might have different influence on liver microenvironment and this might explain the conflicting results between studies.

If altered immune microenvironment affects tumor

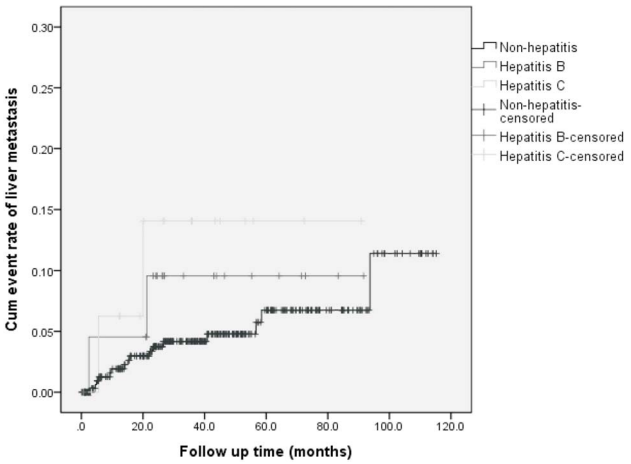

Fig. 4. Subgroup analysis of liver metastasis rate after diagnosis.

cell metastasis, we might observe similar phenomenon in other malignancies. Other than CRC, few studies aimed on the influence of hepatitis on liver metastasis. In pancreatic cancer, there were 2 studies aimed to verify the effects of hepatitis on liver metastasis which showed contrary results.[18,19] In conclusion, whether changes in liver-associated immunity contribute to the impediment of cancer cell colonization remains unclear.

There were some limitations noted in our study. First, the rare events of hepatitis and liver metastasis were noted in this study, further study with larger sample size may be needed. Second, because of the retrospective setting of this study, not every patient included have serologic assay for hepatitis viral infection approval. Third, patient with hepatitis carries a higher incidence for developing hepatocellular carcinoma, which may not differentiate from metastatic lesion if no tissue available for pathological approval. This may lead to misjudgment of liver metastasis.

In conclusion, in our study, chronic hepatitis infection did not have significant influence on incidence of liver metastasis in CRC patients. Patient with chronic hepatitis may have a tendency to have higher risk of developing metachronous liver metastasis. No difference were found in overall survival between the two groups.

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原　著

肝炎和大腸直腸癌肝臟轉移之間的關係

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目的　在大腸直腸癌的病人中，有慢性肝炎的病人在之前的研究中顯示較低的機會發生肝臟轉移。但在最近的全國性研究發現，慢性肝炎合併肝硬化的這群病人反而有較高的機會發生肝臟轉移。我們的研究想要探討慢性肝炎和大腸直腸癌肝臟轉移的關係。

方法　我們統計了 2006 年 1 月至 2015 年 12 月 565 位在基隆長庚醫院診斷為大腸直腸癌併接受治療的病人。我們回顧性收集了病人的病歷資料，包括影像、病歷、實驗室檢查。HBsAg 陽性及 Anti-HCV 陽性的病人被定義為慢性肝炎。Chi square test 和 Student t test 被用於比較兩組的基本資料和發生肝臟轉移的風險。Kaplan-Meier method 被用於存活分析併使用 log-rank test 比較兩組。

結果　所有的病人中，實驗組的 54 位是被定義為慢性肝炎，其餘 464 位則是無慢性肝炎。有 104 位病人發生肝臟轉移，包括 82 位診斷時就發生肝臟轉移，以及 22 位在追蹤過程中發現肝臟轉移。兩組病人在診斷時發生肝臟轉移的機率無顯著差異，慢性肝炎的病人在追蹤過程中有較高的機會發生肝臟轉移。兩組的病人的存活率無差異。

結論　慢性肝炎對大腸直腸癌的肝臟轉移以及存活率並無顯著的影響。在追蹤的過程中可能有較高的機會發生肝臟轉移。兩組的存活率沒有差異。

關鍵詞　大腸直腸癌、慢性肝炎、B 型肝炎、C 型肝炎、肝臟轉移。