Chinese-German J Clin Oncol
DOI 10.1007/s10330-014-1298-z
May 2014, Vol. 13, No. 5, P212–P214

Relationship between hepatitis B virus infection and hepatic metastasis in non-small cell lung cancer

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Received: 23 February 2014 / Revised: 27 March 2014 / Accepted: 15 April 2014
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Abstract ***Objective:*** The purpose of the study was to explore the relationship between hepatitis B virus (HBV) infection and hepatic metastasis in non-small cell lung cancer (NSCLC). ***Methods:*** Four hundred and eighty cases of NSCLC were retrospectively analyzed from January 2003 to January 2010, and the prevalence of hepatic metastasis of NSCLC in patients with and without hepatitis B virus infection were compared. ***Results:*** In the HBV carriers' group, the prevalence of synchronous hepatic metastasis and metachronous hepatic metastasis were 13.2% and 5.9%, respectively. Meanwhile in the non-HBV group, those were 21.6% and 9.5% respectively. A significant difference between the two groups was found ($P < 0.05$). ***Conclusion:*** The prevalence of synchronous hepatic metastasis and metachronous hepatic metastasis in non-small cell lung cancer with HBV infection are lower than those in non-HBV infection group. Hepatic metastasis is infrequent in HBV infected cases of NSCLC.

Key words hepatitis B virus (HBV); non-small cell lung cancer (NSCLC); hepatic metastasis

Hepatic metastasis of lung cancer is the most common blood-borne metastasis, ranking No. 3 in liver metastatic carcinoma. In order to discuss the relationship between Hepatitis B virus (HBV) infection and hepatic metastasis in non-small cell lung cancer (NSCLC), 480 cases of NSCLC were retrospectively analyzed from January 2003 to January 2010 in the Third Hospital of Mianyang (China) and the Central Hospital of Mianyang (China), and the prevalence of hepatic metastasis of NSCLC in patients with and without HBV infection were compared.

Patients and methods

Patients characteristics

The group of NSCLC patients investigated included 480 (354 males and 126 females). The mean age was 58.1 years (range, 34–78 years). The diagnosed NSCLC were confirmed pathologically via bronchofibroscopy, lung puncture and surgery, including 307 cases of squamous cell carcinoma, 172 cases of adenocarcinoma, adenosquamous carcinoma in 1 case. 68 cases of HBsAg positive (infection group) and 412 cases of HBsAg negative (non-infection group) were shown in Table 1.

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Hepatic metastasis

There were 141 patients with hepatic metastases among 480 cases of NSCLC, including synchronous hepatic metastasis in 98 cases, and metachronous hepatic metastasis in 43 cases. Alpha-fetoprotein was normal. 9 cases of HBV infection with synchronous hepatic metastasis and 4 cases of HBV infection with metachronous hepatic metastasis were included, and the average time of metachronous metastasis was 6 months. Meanwhile non-infectious group with synchronous hepatic metastasis were 89 cases, and 39 cases with metachronous hepatic metastasis. 134 cases of hepatic metastasis were diagnosed by CT or B-ultrasound, and the other 7 cases were confirmed pathologically via intraoperative exploration. Cases were as follows: 33 cases of single metastatic nodules, 48 cases of 2–4 metastatic nodules, 60 cases of more than 5 metastatic nodules.

Other metastases (brain metastases, bone metastases and so on): bone metastases in 21 cases, and lung metastases in 37 cases.

Statistical analysis

χ^2 was employed to compare hepatic metastasis and extrahepatic metastasis, and analysis was performed using the SPSS 12.0. Differences were considered significant at $P < 0.05$.

Table 1 Clinical data of the 480 patients in HBsAg (+) group and HBsAg (–) group (*n*)

Item	HBsAg (+) group	HBsAg (–) group	*P*
Sex			
Male	49	305	< 0.05
Female	19	107	
Age (years)			
Range	34–76	40–78	< 0.05
Median age	57.8	60	
Pathological types			
Squamous cell carcinoma	42	265	< 0.05
Adenocarcinoma	26	146	
Adenosquamous carcinoma	0	1	
Location			
Central	54	326	< 0.05
Peripheral	14	86	

Results

HBsAg and hepatic metastasis in NSCLC

In the HBsAg (+) group, the prevalence of synchronous hepatic metastasis and metachronous hepatic metastasis in NSCLC were 13.2% and 5.9%, respectively, which were significantly lower than 21.6% and 9.5% in the HBsAg (–) group ($P < 0.05$; Table 2).

HBsAg and extrahepatic metastases in NSCLC (brain metastases, bone metastases and so on)

The relationship between HBsAg and extrahepatic metastases in NSCLC (brain metastases, bone metastases and so on) was shown in Table 3. There was no statistical difference between HBsAg (+) group and HBsAg (–) group ($P > 0.05$).

Discussion

Hepatic metastases of squamous cell carcinoma and adenocarcinoma in NSCLC accounted for approximately 23% and 17%, respectively [1]. The illness progress was rapid, and partial patients with liver metastasis from lung cancer would die within seven months. Hepatic metastasis of lung cancer was affected by many factors. In addition to pathological type and differentiation of primary tumors, liver itself was also one of most important factors. Uetsuji *et al* [2] reported that liver metastasis of colorectal cancer in the HBVAg (+) group accounted for 10%, and 34. 3% in the HBVAg (–) group. And Utsunomiya *et al* [3] reported liver metastasis rate in colorectal cancer with Hepatitis B or C virus infection was 8.1%, which was significantly lower than 21.1% with non infection. The results in this study also show that the incidence of liver metastasis in NSCLC with HBV infection is lower. It can be considered that pathological changes of livers with HBV infection have an impact on liver metastasis in NSCLC, and HBV infection may be a protective factor to reduce liver metastasis in NSCLC.

The low prevalence of hepatic metastasis in HBV infection group may be associated with the immunologic mechanism of the infected liver. A large number of kupffer cells located on the hepatic sinusoidal endothelial cells are actually fixed sessile phagocytes. Research has shown that kupffer cells can eliminate or weaken the antigenicity. The activated kupffer cells can promote the apoptosis of experimental hepatoma carcinoma cell [4]. Killer cells in the lymphatic system, such as natural killer cells, lymphokin activated killer cells and killer T cells, are activated when infected. The direct cytotoxic effect of effector cells and lymphotoxin induced by HBV maybe play a certain role in killing a small amount of cancer cells which supply blood to the liver. In addition to swallowing function, macrophages could produce some immunomodulatory factors, such as interferon, prostaglandin. And interferon plays an important role in the treatment of anti-tumor. Research based on a large number of trial studies has supported that hepatitis virus infection directly stimulates the activation of hepatic sinusoidal endothelial cells, Kupffer cells, monocytes, and produces IL-6. IL-6 has strong promotion of fat storing cells proliferation, and increases the total synthesis of liver extracellular matrix.

Table 2 Synchronous hepatic metastasis and metachronous hepatic metastasis in NSCLC with HBV infection

Group	Total	Synchronous hepatic metastasis		Metachronous hepatic metastasis	
		n	%	*n*	%
HBsAg (+) group	68	9	13.2	4	5.9
HBsAg (–) group	412	89	21.6	39	9.5

Table 3 Brain metastases and bone metastases in NSCLC with HBV infection

Group	Total	Brain metastases		Osseous metastases	
		n	%	*n*	%
HBsAg (+) group	68	13	19.1	18	26.5
HBsAg (–) group	412	87	21.1	101	24.5

Furthermore, it also promotes the expression of α-macroglobulin, and inhibits collagenase activity, resulting in the intrahepatic collagen deposition and inhibiting the formation of carcinoma metastaticum. When HBV is infected, cellular immune function is disordered [5], helper lymphocyte T and suppressor T lymphocytes function are enhanced, so that metastasized tumor cells can be eliminated easily.

In addition, liver damage and cirrhosis after HBV infection may be unfavorable factors of liver metastasis in NSCLC. The possible mechanism remains as follows: liver fibrosis at the time of liver cirrhosis and the distorted hepatic vascular are not conducive to the metastasis of cancer cells. The relative reduction of intrahepatic blood flow causes the number of liver cancer cells to be reduced. Gervaz *et al* [6] summarized from 1976 to 2001 cirrhosis patients with colon cancer confirmed by laparotomy was found only l0% in the liver metastases, which indicated that colorectal cancer was not easy to metastasize to hardening livers. The results are similar to the investigation in this article.

In conclusion, the results of this study show that NSCLC less metastasizes to the liver with HBV infection while there are no significant differences in brain metastases and bone metastases between HBsAg (+) group and HBsAg (–) group, which makes a similar report with previous studies on colorectal hepatic metastasis with HBVAg positive. The data have indicated that hepatic metastasis of NSCLC is inhibited to some extent when HBV is infected. However, this study is a retrospective analysis. HBsAg (+) can only show patients have ever been infected with HBV. We are unable to know how virus replication titer is because a considerable part of patients have not checked. It need to be proved whether virus replication titer has an impact on the results. Furthermore, these are the statistical results of Mianyang, and it is unknown whether there are regional differences. Further clinical research need to be done in the future.

References

1. WB Yin, ZH Yu, GZ Xu, *et al*. Radiation oncology. Beijing: Peking Union Medical College press, 2008. 581.
2. Uetsuji S, Yamamura M, Yamamichi K, *et al*. Absence of colomctsl cancer metastasis to the cirrhotic liver. Am J Surg, 1992, 164: 176–l77.
3. Utsunomiya T, Saitsu H, Saku M, *et al*. Rare occllrrence of colorectal cancer metastasis in Livers infected with hepatitis B or c vires. Am J Sury, 1999, 177: 279–281.
4. Zhu HZ, Ruan YB, Wu ZB. The influence of kupffer cells on the expression of apoptosis related genes in experimental hepatocellular carcinoma. J Tongji Med Univ, 2000, 29: 97–99.
5. He DH, Zhan PZ. Hepatobiliary pathology. Shanghai: Second Military Medical University Press, 1997. 129.
6. Gervaz P, Pakart R. Colorectal adenoearcinoma in cirrhotic patients. J Am Coll Surg, 2003, 196: 874–879.