

## Original Article

# Unusual extrahepatic metastatic sites from hepatocellular carcinoma

Tadashi Terada<sup>1</sup>, Hirotohi Maruo<sup>2</sup>

Department of <sup>1</sup>Pathology and <sup>2</sup>Surgery, Shizuoka City Shimizu Hospital, Shizuoka, Japan

Received November 25, 2012; Accepted March 27, 2013; Epub April 15, 2013; Published April 30, 2013

**Abstract:** The author examined unusual extrahepatic metastatic sites from liver hepatocellular carcinomas (HCCs) in autopsy and surgical files at our laboratory in the last 10 years. In autopsy cases (n=31), extrahepatic metastases were present in 21 cases (68%). The most common metastatic sites were lung (n=18). Unusual extrahepatic metastatic sites in the autopsy series were abdominal regional lymph nodes (n=6), bones (n=5), diaphragm (n=2), pancreas (n=2), gall bladder (n=1), stomach (n=1), colon (n=1), adrenal gland (n=1), pleura (n=1), peritoneum (n=1), cervical lymph nodes (n=1), and shoulder soft tissue (n=1). In surgical cases (n=21), in which extrahepatic tumors were excised, the lung was the most common, and accounted for 16 cases. The unusual extrahepatic metastatic sites in the surgical series were bones (n=2), brain (n=1), skin (n=1), and oral cavity (n=1). Immunohistochemical demonstration of HepPar1 and AFP were recognized in 12 of 12 surgical cases examined and 8 of the 12 surgical cases examined, respectively. Cytokeratin 8 and 18 were expressed in 6 of 6 surgical cases and 7 of 7 surgical cases examined. These data shows that HCC can metastasize in various organs other than the lung, and HepPar1 and AFP were good markers of extrahepatic metastases of these unusual sites of metastatic foci from HCC.

**Keyword:** Hepatocellular carcinoma, metastasis, autopsy, surgery, pathology

## Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancy in the world. HCC is associated hepatitis C virus (HCV), hepatitis B virus (HBV), other hepatitis viruses, autoimmune hepatitis, steatohepatitis, and primary biliary and sclerosing cholangitis. Most of the liver with HCC was complicated by cirrhosis. Cirrhosis is the cause of portal hypertension and liver failure. HCC shows intrahepatic multiple occurrence and intrahepatic metastasis. The site of extrahepatic metastasis of HCC is mostly the lung [1-4]. Extrahepatic metastasis of HCC occurs in about 30-50% of patients, and it depends on HCC stages [1-4]. Extrahepatic metastases to unusually sites from HCC have been reported in a few case reports [5-20]. The author herein examined the unusual extrahepatic metastatic sites from hepatic HCC.

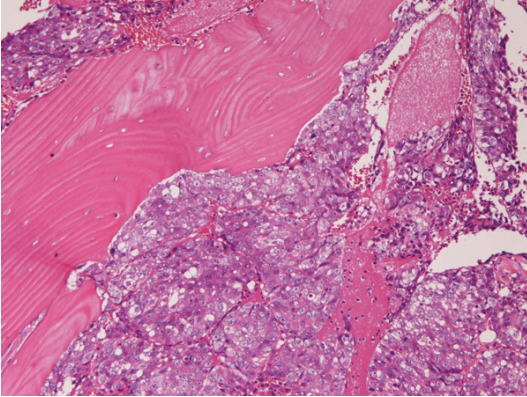
## Materials and methods

The author has performed 311 autopsies during the last 10 years. Thirty-one cases of the

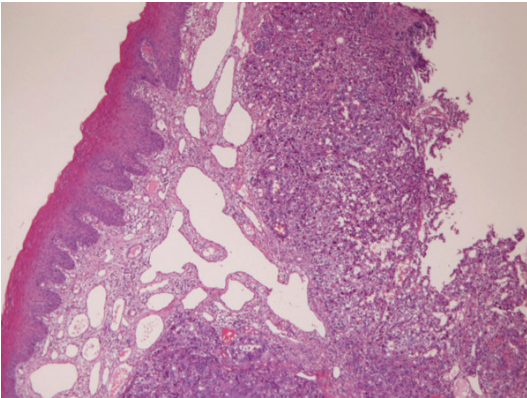
311 were HCC. The autopsy and clinical records of these 31 cases of HCC were obtained, and re-examined macroscopically and microscopically. Of the 31 cases of HCC, 23 were associated with HCV, and 5 with HBV, and 1 with autoimmune hepatitis. The etiology of the remaining 2 was unknown. Of the 31 cases, 28 were complicated by liver cirrhosis, and 3 by chronic hepatitis or autoimmune hepatitis. Portal tumor thrombi were recognized in 12 cases. Portal hypertension was noted in 29 cases. The age of the patients ranged from 50 to 94 years with a median of 63 years. Male to female ratio was 28:3.

The author also diagnosed extrahepatic metastasis of HCC in 21 cases of surgically resected specimens. The pathologic reports and clinical records were obtained, and the author re-examined the surgical specimens. Of the 21 cases, 19 had been diagnosed as HCC, but the remaining 2 cases were not diagnosed as HCC. The latter two cases, the extrahepatic metastatic sites were the first manifestations of HCC. The age ranged from 45 to 76 years

## Metastases of HCC



**Figure 1.** The bone metastasis of hepatocellular carcinoma. HE, x100.

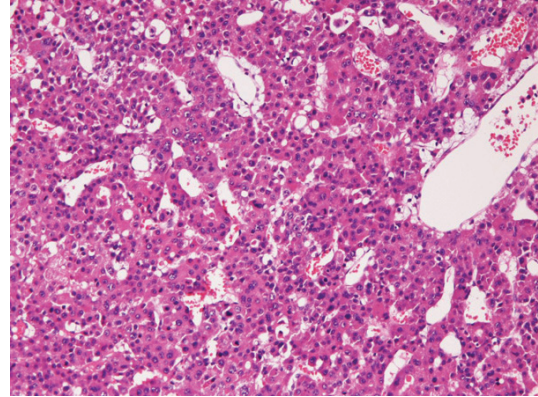


**Figure 2.** Oral cavity (gingival) metastasis of hepatocellular carcinoma. HE, x50.

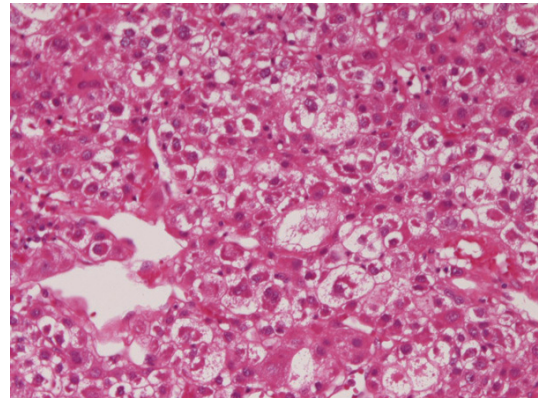
with a median of 57 years. The male to female ratio was 15:6. Of the 21 surgical cases, 19 were complicated by cirrhosis, and the remaining 2 with chronic hepatitis. Of the 21 cases, anti-HCV was positive in 18 cases and HBs antigen was positive in 3 cases. Clinically, portal hypertension was recognized in 16 cases.

### Results

In autopsy cases (n=31), extrahepatic metastases were present in 21 cases (68%). The most common metastatic sites were lung (n=18). Unusual extrahepatic metastatic sites in the autopsy series were abdominal regional lymph nodes (n=6), bones (n=5), diaphragm (n=2), pancreas (n=2), gall bladder (n=1), stomach (n=1), colon (n=1), adrenal gland (n=1), pleura (n=1), peritoneum (n=1), cervical lymph nodes (n=1), and shoulder soft tissue



**Figure 3.** Extrahepatic metastasis of moderately differentiated hepatocellular carcinoma. Trabecular and pseudoglandular arrangements and acidophilic cytoplasm are recognized. HE, x200.



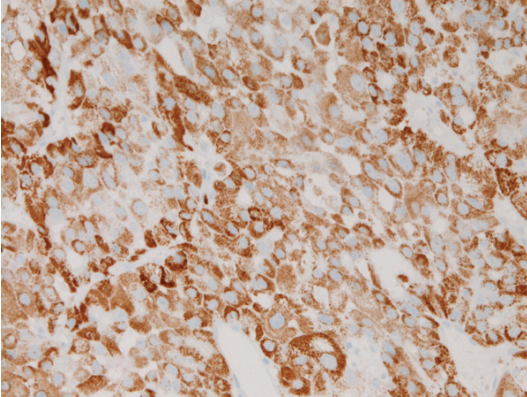
**Figure 4.** Numerous Mallory bodies are seen in a skin metastasis of hepatocellular carcinoma. HE, x200.

(n=1). Histologically, of the 21 cases, extrahepatic metastatic sites were well differentiated HCC in 5 cases, moderately differentiated HCC in 9 cases, and poorly differentiated HCC in 7 cases.

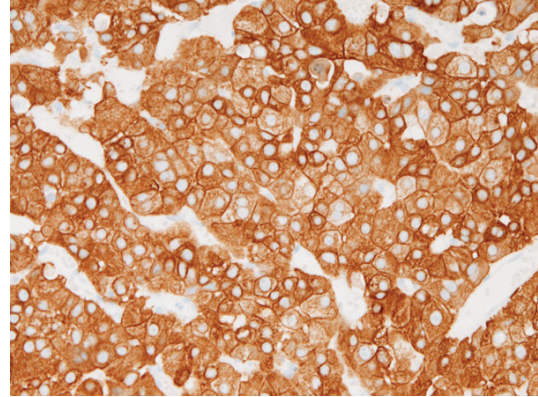
In surgical cases (n=21), the lung was the most common metastatic site, and accounted for 16 cases. The unusual extrahepatic metastatic sites in the surgical series were bones (n=2) (**Figure 1**), brain (n=1), skin (n=1), and oral cavity (n=1) (**Figure 2**). The metastatic sites of the 2 cases (skin and oral cavity) were the first manifestations of HCC. The metastatic sites was well differentiated HCC in 6 cases, moderately differentiated HCC (**Figure 3**) in 7 cases, and poorly differentiated HCC in 8 cases. Numerous Mallory bodies were seen in 1 case (**Figure 4**). The author performed an



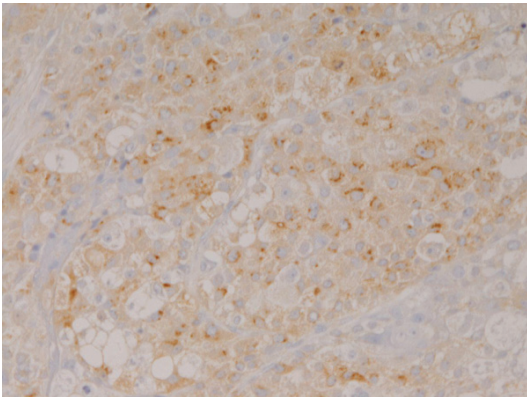
## Metastases of HCC



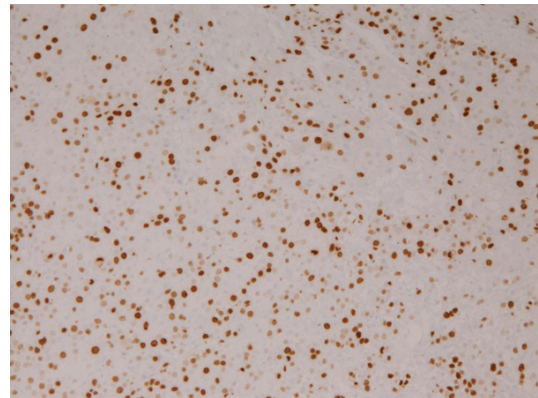
**Figure 5.** HepPar1 is strongly positive in an extrahepatic metastasis in the cervical lymph node. Immunostaining, x200.



**Figure 7.** Cytokeratin 18 is positive in an extrahepatic metastasis of the lung. Immunostaining, x200.



**Figure 6.** AFP is positive in a brain metastasis from HCC. Immunostaining, x200.



**Figure 8.** Ki-67 labeling was 87% in this extrahepatic metastasis of the brain. Immunostaining, x200.

immunohistochemical study in the surgical cases, with the use of Dako Envision method (Dako Corp, Glostrup, Denmark), as previously reported [21-28]. The antibodies were HepPar 1 (OCH1E5, Dako), AFP (polyclonal, Dako), cytokeratin 8 (35BH11, Dako), cytokeratin 18 (DC10, Dako), p53 protein (D07, Dako), and Ki-67 (MIB1, Dako). HepPar1 (**Figure 5**) and AFP (**Figure 6**) were positive in 12 of 12 surgical cases examined and 8 of the 12 surgical cases examined, respectively. Cytokeratin 8 and 18 were expressed in 6 of 6 surgical cases and 7 of 7 surgical cases (**Figure 7**). p53 protein was positive in 8 of the 14 cases examined, and high Ki-67 labeling (labeling: from 21% to 76%) was positive in all cases (**Figure 8**).

### Discussion

Extrahepatic metastasis of HCC occurs in about 30-50% of HCC cases [1-4]. The most

common metastatic sites are lung, and less frequently in the lymph nodes and bones [1-4]. In autopsy series, Sawabe et al [1] examined extrahepatic metastases of HCC in 98 autopsy cases, and found that 64% had extrahepatic metastases, and most of them (97%) were pulmonary metastases. In living patients, Katyal et al [2] found extrahepatic metastasis in 148 (32%) of the 463 patients with HCC. The most common sites were lung (55%), followed by lymph nodes (41%) and bones (28%); the percentage was that of positive cases [2]. Natsuzaka et al [3] reported that 65 (13%) of the 482 patients with HCC had extrahepatic metastases. The most common location was lung, followed by bone and lymph nodes [3]. Watanabe et al [4] demonstrated that abdominal regional lymph node metastasis of HCC was found in 168 (26%) of the 660 autopsy cases of HCC. He et al [5] reported 205 cases of HCC with bone metastasis. Fukutomi et al [6]

collected 673 patients with HCC and reported that the site of bone metastases from HCC was most frequent in vertebra, followed in order by pelvis, rib, and skull. These extrahepatic metastases of lung, bones and lymph nodes are more frequent in the advanced stages than in the early stages [1-6].

In the present autopsy cases, extrahepatic metastases were present in 21 of the 31 cases (68%). The most common metastatic sites were lung (n=18). Regional lymph nodes metastases were found in 6 cases (19%), and bone metastases were found in 5 cases (16%). In the present surgical cases, lung metastases were 16 cases, and bone metastases were 2 cases. These findings indicate that the most common extrahepatic metastasis site is lung, as in the previous studies [1-4]. In the present case, bone and lymph nodes metastases were relatively infrequent, indicating that bone and lymph nodes are unusual sites of extrahepatic metastasis of HCC.

In the present, unusual metastatic sites from HCC were recognized. They were diaphragm (n=2), pancreas (n=2), gall bladder (n=1), stomach (n=1), colon (n=1), adrenal gland (n=1), pleura (n=1), peritoneum (n=1), cervical lymph nodes (n=1), shoulder soft tissue (n=1), brain (n=1), skin (n=1), and oral cavity (n=1). These data indicate that HCC can metastasize in any locations.

There are only a few case reports of each unusual metastatic site from HCC; in the diaphragm [7], in the pancreas [8], in the gall bladder [9], in the stomach [10], in the colon [11], in the adrenal gland [12], in the pleura [13], in the peritoneum [14], in the cervical lymph node [15], in the soft tissue [16], in the brain [17], in the skin [18, 19], and in the oral cavity [20]. It was very interesting that the metastatic sites of the present 2 cases (skin and oral cavity) were the first manifestations of HCC.

The pathological diagnosis of metastatic HCC in extrahepatic metastatic site can be made relatively easily in patients with HCC. The histologies of HCC show trabecular and pseudoglandular patterns composed of acidophilic cells. Detection of bile is confirmative for HCC. Mallory bodies strongly suggest HCC. However, immunohistochemical studies are of great value. HepPar1 is a relatively specific marker of

hepatocytes and HCC [29]. AFP is a specific marker of HCC and Yolk sac tumor. As is well known, cytokeratins 8 and 18 are hepatocyte cytokeratins, but they are expressed in other tumors. P53 expression indicated p53 mutations, and a marker of malignancy [30]. Ki-67 labeling indicates cell proliferative activity. In the present study, HepPar1 and AFP were very useful in the adjunct diagnosis of HCC. Cytokeratins 8 and 18 were helpful in HCC diagnosis. P53 expression and high Ki67 labeling were useful tools of malignant nature of HCC.

In summary, the present data shows that HCC can metastasize in various organs other than the lung, and HepPar1 and AFP were good markers of extrahepatic metastases of these unusual sites of metastatic foci from hepatic HCC.

### Declaration

The author has no conflict of interest.

**Address correspondence to:** Dr. Tadashi Terada, Department of Pathology, Shizuoka City Shimizu Hospital, Miyakami 1231 Shimizu-Ku, Shizuoka 424-8636, Japan. Phone: 81-54-336-1111; Fax: 81-54-336-1315; E-mail: piyo0111jp@yahoo.co.jp

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