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Brain Metastasis from Hepatocellular Carcinoma after Radical Hepatectomy

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ABSTRACT

Brain metastasis from hepatocellular carcinoma (HCC) is a rare, yet perplexing problem in patients with cancer. We report on 5 patients with metastasis of HCC to the brain after radical hepatectomy. Intrahepatic recurrence occurred in 3 patients, and distant metastasis to sites other than the brain was observed in 3 patients (lung, 2; bone, 1). The symptoms for brain metastasis included headache, hemiparesis, and vomiting. Hemorrhage was found in 4 of 5 patients. All patients had a single nodular lesion in the brain. The alpha-fetoprotein levels were more than 10,000 ng/ml in 4 patients. Two patients underwent surgical resection, 1 received cranial irradiation, and 2 were administered corticosteroids. The interval between diagnosis of the primary cancer and detection of brain metastasis ranged from 2 to 54 months. The mean survival period was only 3 months after diagnosis of brain metastasis. All 5 patients died of neurologic causes. Because no effective treatment for brain metastasis from HCC is available, further study is needed.

Key words: *Hepatocellular carcinoma, Brain metastasis, Hepatectomy*

The development of diagnostic techniques such as computed tomography (CT), ultrasonography, and angiography have contributed to earlier diagnosis of hepatocellular carcinoma (HCC) and improved chances for tumor resection. Sophisticated surgical techniques have lowered operative mortality. Furthermore, improved perioperative management and better evaluation of liver function have decreased the incidence of postoperative liver failure. Consequently, the number of long-term survivors after hepatectomy has increased recently. However, the incidence of recurrence, the main cause of death in HCC, remains high, and most patients have a poor outcome. The most frequent pattern of recurrence is intrahepatic. In patients with extrahepatic metastasis, pulmonary and bone metastases sometimes occur, whereas brain metastasis is extremely rare. Nevertheless, brain metastasis remains a perplexing problem in patients with cancer. Here, we describe our experience with 5 patients with metastasis of HCC to the brain.

PATIENTS AND METHODS

Between 1986 and 1997, a total of 374 patients with HCC underwent hepatectomy at the Department of Surgery II, Hiroshima University School of Medicine. Brain metastasis was diagnosed, after radical hepatectomy, in 5 of these patients who were followed up both at our department and at other medical facilities. The serum alpha-fetoprotein (AFP) level and prothrombin-induced vitamin K agonist II (PIVKA-II) level were measured every month, ultrasonography was done every 3 months, and computed tomography (CT) and chest X ray examination were performed every 6 months in all patients. Bone scintigraphy and brain CT were performed when necessary. Recurrence was diagnosed on the basis of the above examinations. Brain metastasis was confirmed by brain CT or by pathologic examination of tissue obtained at the time of tumor resection. We evaluated clinical and pathological factors according to The General Rule for the Clinical and Pathological Studies of Primary Liver Cancer, 3rd edition, Liver Cancer Study Group of Japan. The cause of death was determined by assessing the status of both systemic and central nervous system disease within 1 month after death.

RESULTS

Clinical characteristics of patients (Table 1). The patients were 3 men and 2 women (age 43 to 77 years). Serological tests for serum hepatitis B virus surface antigen were positive in 1 patient, and serum anti-hepatitis C virus antibody was present in 4 patients. All patients concurrently had liver cirrhosis. Four patients had a single tumor, and 1 had a multiple tumor in the liver. The AFP level was more than 50, 000 in 2 of the 5 patients.

Primary hepatectomy and pathological findings (Table 2). Surgical procedure ranged from partial resection to segmentectomy. All tumors showed capsule formation, and cancer cells infiltrated the capsules of 2 of the 5 patients. Two tumors invaded the portal vein, including one that invaded also the hepatic vein and metastasized intrahepatically.

Intrahepatic recurrence (Table 3). Three patients had intrahepatic recurrence and had received various kinds of treatment, including transcatheter arterial infusion chemotherapy (TAIC), percutaneous microwave coagulation therapy (PMCT), percutaneous ethanol injection therapy (PEIT), and hepatic resection.

Distant metastasis to sites other than the brain (Table 3). Lung metastasis was diagnosed in 2 patients, who subsequently underwent pulmonary resection. Bone metastasis was diagnosed in 1 patient, and he received radiotherapy. Two patients showed no evidence of extracerebral metastases.

Brain metastasis (Table 4). Brain metastasis was diagnosed within a year after primary hepatectomy in 2 patients. In the 3 other patients, brain metastasis developed more than 5 years after hepatectomy with resection of their primary lesions. The most frequent symptoms of brain metastasis were: headache (3 patients), hemiparesis (1), and vomiting (1). Hemorrhage was found in 4 patients. All patients had a single nodular lesion in the brain, located in the temporal (2 patients), parietal (2), or occipital (1) regions. The serum AFP level was more than 10, 000 in 4 patients at the time of diagnosis of brain metastasis. Two patients underwent surgical resection, which was palliative, not curative. The main objective of surgery was to drain hematomas due to hemorrhage. One patient received cranial irradiation, and 2 received corticosteroid therapy (usually dexamethasone). The interval between diagnosis of

Table 1. Clinical characteristics of patients with primary HCC

Case	Age (yrs)	Sex	HBs-Ag	HCV-Ab	Associated liver disease	Number of tumors	Tumor size (cm)	AFP (ng/ml)
1	66	Female	(–)	(+)	Cirrhosis	Single	4	22.9
2	58	Female	(–)	(+)	Cirrhosis	Single	3.8	12.9
3	43	Male	(–)	(+)	Cirrhosis	Single	2	574.0
4	77	Male	(–)	(+)	Cirrhosis	Single	5.3	74007.1
5	48	Male	(+)	(–)	Cirrhosis	Multiple	10	511205.0

HBs-Ag, hepatitis B surfave antigen; HCV-Ab, hepatitis C virus antibody; AFP, alpha-fetoprotein

Table 2. Procedure for primary hepatectomy and pathological findings

Case	Operation	Edmondson Grade	fc	fc-inf	vp	vv	IM
1	Partial hepatectomy	III	(+)	(–)	(–)	(–)	(–)
2	Segmentectomy	III	(+)	(+)	(+)	(–)	(–)
3	Partial hepatectomy	II	(+)	(–)	(–)	(–)	(–)
4	Segmentectomy	II	(+)	(+)	(–)	(–)	(–)
5	Segmentectomy	II	(+)	(–)	(+)	(+)	(+)

fc, fibrous capsular formation; fc-inf, cancer cell infiltration into fibrous capsule; vp, cancer cell invasion into the portal vein; vv, cancer cell invasion into the hepatic vein; IM, intrahepatic metastasis

Table 3. Patients with intrahepatic recurrence and distant metastasis, excluding the brain

Case	Intraheatic recurrence		Distant metastasis		
	interval to brain metastasis (mos)	Treatment	Location	Interval to metastases (mos)	Treatment
1	18	TAIC, hepatectomy, PEIT	lung	48	Resection
2	26	TAIC, PMCT	lung	4	Resection
3	42	TAIC, hepatectomy	bone	2	Radiotherapy

TAIC, transcatheter arterial infusion chemotherapy; PEIT, percutaneous ethanol injection therapy; PMCT, percutaneous microwave coagulation therapy

Table 4. Profile of patients with brain metastasis

Case	Sympton	Location	Hemorrhage	AFP level (ng/ml)	Treatment	Interval to brain metastasis (mos)	Interval from brain metastasis to death (mos)
1	Headache	Temporal	(+)	193380	Resection	48	2
2	Headache	Occipital	(+)	11000	Conservative	54	2
3	Headache	Temporal	(+)	46598	Conservative	51	2
4	Paresis	Parietal	(+)	14471	Resection	12	6
5	Vomiting	Parietal	(–)	280	Radiotherapy	2	3

AFP, alpha-fetoprotein

the primary cancer and diagnosis of brain metastasis ranged from 2 to 54 months. The overall median duration of survival after the diagnosis of brain metastasis was only 3 months (2–6 months). All 5 patients died of neurologic causes.

Course of brain metastasis. The clinical course of each of the 5 patients are shown in Fig. 1. In 3 patients, hemorrhage preceded the diagnosis of brain metastasis. Intrahepatic recurrence occurred in case 1, 2 and 3, and these patients received TAIC with secondary hepatic resection or PMCT. Despite intensive treatment, the serum AFP level did not decrease. Hemorrhage occurred, leading to the diagnosis brain metastasis. Pulmonary metastasis occurred in case 4, and the patient underwent pulmonary resection. However, the serum AFP level remained elevated. The diagnosis of brain metastasis was preceded by hemorrhage.

DISCUSSION

Brain metastases are a major cause of mortality in patients with cancer. They usually occur late in the disease, and are sometimes associated with widespread systemic metastases.

In HCC, the lungs and bone are the most frequent sites of extrahepatic metastasis. Brain metastasis from HCC is rarely reported and is usually diagnosed in end-stage metastatic disease. The Japanese Liver Cancer Study Group estimated that the incidence of brain metastasis from HCC is 0.7% clinically and 2.9% at autopsy[5]. The Brain Tumor Registry of Japan reported that only 1.2% of metastatic brain tumors arise from HCC[2]. Our department has diagnosed brain metastasis in 5 of 374 cases of HCC (1.3%). Several explanations may account for the apparent rarity of brain metastasis. Cancer cells traveling by hematogenous spread are filtered by the lungs, so that brain metastasis may occur secondarily to pulmonary lesions. It is also possible that most patients with HCC die before brain metastasis arises or becomes symptomatic. Perhaps, HCC cells share little in common with brain tissue [1,13,15].

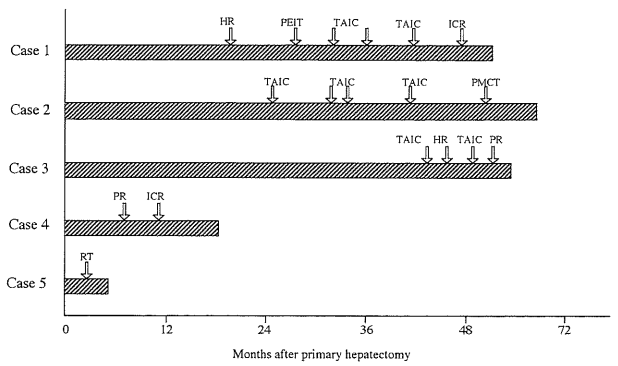

Fig. 1. Clinical course of each of 5 patients with brain metastasis after primary hepatectomy.
HR, hepatic resection; PEIT, percutaneous ethanol injection therapy; TAIC, transcatheter arterial infusion chemotherapy; ICR, intracranial resection; PMCT, percutaneous microwave coagulation therapy; PR, pulmonary resection; RT, radiotherapy.

At presentation, the most common neurologic symptoms associated with brain metastasis from HCC were similar to those caused by other metastatic brain tumors and included headache, nausea, and hemiparesis. The majority of patients with brain metastases also have concomitant systemic metastases, especially in the lungs[6,13,14]. Because HCC most likely metastasizes to the lung via the hepatic venous system, brain metastases are believed to occur via the lungs. In contrast to other metastatic brain tumors, however, brain tumors from HCC often cause hemorrhage. Sometimes, the primary tumor is not diagnosed before the onset of hemorrhage[4,11]. Three of our patients had hemorrhage before the diagnosis of brain metastasis. HCC is highly vascular and most patients with the disease have coagulopathy and thrombocytopenia due to underlying liver cirrhosis. Such patients are thus at increased risk from hemorrhage.

Most patients with HCC and brain metastasis have advanced primary tumors[9], intrahepatic metastases, or extrahepatic metastases[6,13,14]. Brain CT scanning is therefore mandatory in such patients. Even in patients with no evidence of active disease (including primary and metastatic lesions), the presence of a high serum AFP level should alert us to the possibility of brain metastasis.

Most cases of the CT images of brain metastasis from HCC may show hyperdense images on noncontrast CT. The contrast CT scan may disclose homogeneous or ring shape enhancement due to

central necrosis with perifocal edema[16]. The CT images of our four cases were not typical because of hemorrhage. In our study, only one tumor showed ring shape enhancement. We must carefully consider surgical indications for brain metastasis because of its poor prognosis. The characteristics of potential candidates for surgical resection are a single surgically accessible symptomatic tumor, no remaining systemic disease or controlled disease limited to the primary site, good general condition, and a life expectancy of at least 2 months[12]. Recently, stereotactic radiosurgical treatment (SRT) has been widely used to treat metastatic brain tumors[3,8,10]. SRT is noninvasive, requires a shorter hospital stay and is somewhat less expensive than surgery. Mori et al stated that SRT for brain metastasis from renal cell carcinoma in brain disease controled the condition in the majority of patients and was associated with few complications[7]. In addition, Nakagawa et al demonstrated that the 1-year survival rate and survival time in SRT was similar to that in the direct surgical excision group. They postulated, therefore, that SRT can be used for surgical excision of tumors of less than 3.0 cm in diameter and recommended that brain metastases should be treated by SRT or direct surgical resection with systemic chemotherapy[10]. Therefore, early detection and treatment with SRT might provide better survival. Although few studies have used SRT to treat brain metastasis from HCC, SRT should be considered as a treatment option in the future.

The outcome of brain metastasis is extremely poor, irrespective of treatment, and the large majority of patients die of progressive neurologic and systemic disease within 5 months[8]. In our study, the mean survival period after diagnosis of brain metastasis was only 3 months. Surgical resection did not significantly influence survival. Further study is needed to define effective treatment regimens for brain metastasis from HCC.

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