

Pulmonary Metastasectomy for Hepatocellular Carcinoma

Yo-Ju Chen
Han-Shui Hsu
Chih-Cheng Hsieh
Yu-Chung Wu
Liang-Shun Wang
Wen-Hu Hsu
Min-Hsiung Huang
Biing-Shiun Huang

Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Key Words

hepatocellular carcinoma;
lung metastasis;
resection

Background. Hepatocellular carcinoma (HCC) is seldom resectable due to advanced status. Even though hepatectomy is feasible, a large proportional of patients may still develops extrahepatic recurrence. Pulmonary metastasis is the most common site of extrahepatic spread. Few articles have discussed the benefit of resection for lung metastasis after curative hepatectomy. We evaluated the general information and the result of lung resection for patients having lung metastasis after curative resection of HCC.

Methods. Six patients who underwent pulmonary metastasectomy for HCC at Taipei Veterans General Hospital between August 1995 and May 2004 were enrolled in the study. All of them had received the hepatectomy for primary HCC. The demographic information of patients, the site and number of extrahepatic recurrence, the method of surgical intervention and the outcome after surgery were retrospectively reviewed.

Results. There were 4 men and 2 women with the mean age of 47.3 years. All of them were HBV carriers. Five patients had multiple pulmonary metastases removed by wedge resection. Two patients had bilateral lung metastases upon diagnosis of extrahepatic recurrence. The mean duration of follow-up after hepatic resection was 75.0 ± 25.1 months (32 to 104 months). The mean survival after pulmonary resection was 47.2 ± 34.3 months (1 to 94 months). Four patients are still alive and free of the disease. One patient is alive but with the disease. One patient who refused further aggressive treatment after resection of lung metastasis died of the disease 40 months after lung resection, 77 months after hepatic resection.

Conclusions. Lung resection for the pulmonary metastasis of HCC can result in a favorable long-term survival when there is no other intrahepatic or extraphepatic recurrence of HCC. For patients with multiple lung metastases in different lobes or different lungs, aggressive surgical resection is recommended if complete resection can be achieved.

Hepatocellular carcinoma (HCC) is common in Asia and represents the second most common cancer causing death in Taiwan. HCC also accounts for 95% of the cases with primary liver cancer. The mean survival of patients with HCC is less than 1 year. HCC is rarely curable by surgical resection due to the advanced state of the disease when it is diagnosed. Lai *et al* reported that for patients who underwent hepatectomy for large HCC, 64 percents developed recurrence during a median follow-up of 13 months.¹ However, in patients with localized HCC, surgical resection is still the treatment of choice. With the recent advances in diagnostic modalities, perioperative management and surgical technology,

more and more patients are suitable for hepatic resection.² Despite decreasing perioperative morbidity and mortality for hepatic resection, the long-term outcome of patients with HCC is not satisfactory due to a high incidence of recurrence. The predominant type of recurrence is intrahepatic recurrence. Pulmonary metastasis is the most common site of extrahepatic spread.³ Few articles in the English literature have discussed the benefit to the patients who are suitable for resection of lung metastasis after curative hepatectomy. In this study, we retrospectively reviewed the general information and the surgical result of lung resection for lung metastasis of HCC after curative resection of HCC.

Received: June 2, 2004.
Accepted: June 28, 2004.

Correspondence to: Biing-Shiun Huang, MD, PhD, Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, 201, Sec. 2, Shih-Pai Road, Taipei 112, Taiwan.
Tel: +886-2-2875-7546; Fax: +886-2-2873-1488; E-mail: bshuang@vghtpe.gov.tw

METHODS

Between August 1995 and May 2004, 6 patients who had received hepatic resection for HCC underwent lung resection for lung metastasis of HCC in Taipei Veteran General Hospital. The general data including age, sex, preoperative investigations, and the procedures for hepatic and lung resection were retrospectively collected. In addition, the presence of hepatitis B surface antigen, the size of primary HCC and the numbers of pulmonary metastases were also analyzed. All patients were followed up at the outpatient clinic. Chest radiography and liver biochemistry tests were taken at intervals of 1-3 months. Serum α -fetoprotein (AFP) and ultrasonography of the liver were checked on a regular basis during the follow-up period. Whenever indicated, hepatic arteriography was performed to assess intrahepatic recurrence. If chest radiography revealed abnormal lesions, computed tomography of chest was done. In addition, radioisotope image was used to assess extrahepatic recurrence. Patients with pulmonary metastasis and without concurrent intrahepatic recurrence were selected for surgery. Complete resection

was the principle goal and achieved in all patients with lung metastasis. No adjuvant chemotherapy was given but 1 patient who took oral form thalidomide after lung resection for lung metastasis.

RESULTS

The clinical parameters related to hepatocellular carcinoma of these 6 patients are summarized in Table 1. There are 4 men and 2 women with the median age of 41 years. All of them were HBV carriers and 3 had liver cirrhosis (3, 4 and 6). The largest diameter of HCC resected was 15 cm and the smallest one 1 cm. Two patients (3 and 5) developed hepatic recurrence before pulmonary metastases were discovered. The recurrent hepatic tumor was treated by transarterial oily chemoembolization (TAE) respectively before pulmonary resection. The parameters related to pulmonary resection are summarized in Table 2. One patient (3) had only 1 pulmonary metastasis and the others had multiple pulmonary metastases. All of the metastatic lung tumors were removed by wedge resection. Two patients (2

Table 1. The clinical data of the patients with lung metastasis of hepatocellular carcinoma

	Sex	Age	Related liver disease	Size of HCC (cm)	Method of hepatic Resection
1	M	53	Hepatitis B	9	Right lobectomy
2	F	39	Hepatitis B	8	Left lobectomy
3	M	42	Hepatitis B, cirrhosis	1	Left lobectomy
4	M	40	Hepatitis B, cirrhosis	15	Extended right lobectomy
5	F	38	Hepatitis B	8	trisegmentectomy
6	M	72	Hepatitis B, cirrhosis	4	Posterior segmentectomy

Table 2. The location and number of pulmonary metastasis and the operative procedure of pulmonary metastasectomy

Patient No.	Location of lung metastasis	The number of metastatic tumor	Pulmonary resection
1 ^a	RUL, RLL	2	Wedge resection
2	RLL	3	Wedge resection
3	LLL	1	Wedge resection
4 ^b	LUL & LLL	2	Wedge resection
5 ^c	RUL & RML	2	Wedge resection
6 ^a	RLL, LLL	8	Wedge resection

^a The patients had bilateral pulmonary metastases upon the first extrahepatic recurrence was diagnosed.

^b The patient received the second pulmonary resection for local recurrence 4 months later after the first pulmonary operation.

^c The patient received the second pulmonary resection for local recurrence and wide excision for scalp metastasis, about 11 months and 18 months later after the first pulmonary resection.

Table 3. Surgical results of the patients who underwent pulmonary resection for lung metastases of hepatocellular carcinoma

Patient No.	Disease-free Interval (months)	Survival after hepatic resection (months)	Survival after pulmonary resection (months)	outcome
1	10	104	94	Alive, free from disease
2	10	101	91	Alive, free from disease
3	37	77	40	Dead with disease in liver
4	25	60	35	Alive, free from disease
5	10	32	22	Alive with disease in liver
6	75	76	1	Alive, free from disease

and 6) were found to have bilateral pulmonary metastases upon the diagnosis of extrahepatic recurrence. One patient received right thoracotomy followed by left thoracotomy at 1-month interval. The other patient received left thoracotomy first and then right thoracotomy 2 months later. Two patients (4, and 5) developed second pulmonary metastasis and required repeated thoracotomy for resection of metastatic tumors 4 months and 11 months respectively after the first lung operation. One patients (3) developed recurrent disease in liver 14 months after the pulmonary resection. One patient (5) had scalp metastasis 18 months after the first pulmonary resection. The sixth patient had just undergone wedge resection of right lung metastasis 2 months after his first lung operation for left lung metastasis. The mean duration of follow-up after hepatic resection of all 6 patients was 75.0 ± 25.1 months. The mean survival after pulmonary resection of the 6 patients was 47.2 ± 34.3 months. Three patients are still alive with free of the disease. One patient is alive but with the disease. One patient (3) who refused further aggressive treatment for recurrence after resection of lung metastasis died of the disease 40 months after lung resection, 77 months after hepatic resection (Table 3).

DISCUSSION

The recent management strategy and technological advances improved the surgical outcome for patients who had hepatectomy for HCC.^{4,5} However, the recurrence rate of hepatocellular carcinoma is still high after the first successful resection of HCC, up to 80-85% within the first 18 months of hepatectomy.⁶ The incidence of pulmonary metastasis was reported as 8-19%.⁷ Most cases of lung metastasis were detected in the form

of multiple foci coexisting with advanced primary lesions.⁸ There are few English literatures describing the management of this condition. Some investigators considered that further aggressive treatment such as operation was not indicated in the cases of extrahepatic recurrence of HCC since the outcome was poor.⁹ However, some reports suggested that in highly selected patients with isolated extrahepatic recurrence of HCC, surgery was effective in controlling extrahepatic disease and offered the only chance of long-term survival.^{3,10} In our study, among 4 patients who had multiple pulmonary metastases, 1 had recurrent tumors over bilateral lung. The patients who received aggressive pulmonary resection tended to have more favorable long-term results.

In 1991, Sasaki *et al.*⁷ reported that a 55-year-old male patient with HCC developed a solitary pulmonary metastasis in right lung 16 months after hepatic resection for HCC. This patient had lung resection for the metastasis. Ten months later, he underwent left adrenalectomy for another metastasis in the left adrenal gland. In our study, the fifth case was a 38-year-old female who developed pulmonary metastasis about 10 months after the first operation and scalp metastasis 18 months after lung resection. She is still alive now, 32 months after hepatic resection, however, with the recurrent disease of liver.

Sawabe *et al.* analyzed the morphological features of 98 autopsy cases with HCC in relation to pulmonary metastases, and clarified that intravascular invasion and the size of HCC played a significant role in the development of pulmonary metastases. In our study, 4 patients with pulmonary metastasis had the primary hepatocellular carcinoma larger than 8 cm in diameter and only 1 patient had the primary HCC less than 1 cm. Among these patients with larger primary HCC, the median duration from hepatic resection to development of pulmonary metastasis

was 13.8 months, in contrast to 37 months in patient with small primary HCC. A long-term disease-free interval between primary hepatic resection and lung metastasis may predict a favorable outcome following resection of pulmonary recurrence. It remains questionable whether surgery itself really prolongs survival of the disease or a better prognosis can be obtained in this specific group of patients even without any therapy remains questionable. According to our results we had, surgery indeed provided an effective option for those highly selected patients with isolated lung metastasis.

Among other options for the treatment of recurrent HCC, lipiodolization had been advocated as an important modality.¹² Shimada *et al.* suggested that a repeat hepatectomy is the first choice of treatment when the liver function is preserved for surgery, whereas the combined treatment of PEIT and lipiodolization is recommended when re-hepatectomy is not indicated for the recurrent HCC.⁹ Two of our patients with recurrent HCC in liver received TAE.

Some authors recommended the use of adjuvant systemic chemotherapy and careful lifelong follow-up in the patients who had surgery for solitary or occasionally 2 metastases without concomitant intrahepatic recurrence.³ In our series, no patient had adjuvant chemotherapy after either primary hepatic resection or lung resection for metastasis. We observed that patients without previous intrahepatic recurrence before lung metastasis had better prognosis than those with intrahepatic recurrence before lung metastasis developed.

In conclusion, lung resection for the pulmonary metastasis of HCC can result in a favorable long-term survival when there is no other intrahepatic or extraphepatic recurrence of HCC. For patients with multiple lung metastases in different lobes or different lungs, aggressive surgical resection is also recommended if complete resection can be achieved.

REFERENCES

1. Lai ECS, Ng IO, You KT, Choi TK, Fan ST, Mok FP, Wong J. Hepatectomy for large hepatocellular carcinoma: the optimal resection margin. *World J Surg* 1991;15:141-5.
2. Matsuda Y, Ito T, Oguchi Y, Nakajima K, Itzokura T. Rationale of surgical management for recurrent hepatocellular carcinoma. *Ann Surg* 1993;217:28-34.
3. Lo CM, Lai ECS, Fan ST, Choi TK, Wong J. Resection for extrahepatic recurrence of hepatocellular carcinoma. *Br J Surg* 1984;81:1019-21.
4. Lai ECS, Fan ST, Lo CM, Chu KM, Liu CL, Wang J. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. *Ann Surg* 1995;221:291-8.
5. Fan ST, Lai ECS, Ng IOL, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg* 1995;130:198-203.
6. Johnson RC. Hepatocellular carcinoma. *Hepatology* 1997;44:307-12.
7. Sasaki Y, Imaoka S, Shibata T, Wada H, Nagano H, Ishikawa, *et al.* Successful surgical management of pulmonary and adrenal metastases from hepatocellular carcinoma. *Eur J Surg Oncol.* 1991;17:84-90.
8. Levy JI, Geddes EW, Kew MC. The chest radiography in primary liver cancers. *S Afr Med J* 1976;50:1323-6.
9. Shimada M, Takenaka K, Gion T, Fujiwara Y, Kajiyama K, Maeda T, *et al.* Prognosis of recurrent hepatocellular carcinoma: a 10-year-surgical experience in Japan. *Gastroenterology* 1996;111:720-6.
10. Lam CM, Lo CM, Yuen WK, Liu CL, Fan ST. Prolonged survival in selected patients from hepatocellular carcinoma. *Br J Surg* 1998;85:1198-200.
11. Sawabe M, Nakamura T, Kanno J, Kasuga T. Analysis of morphological factors of hepatocellular carcinoma in 98 autopsy cases with respect to pulmonary metastasis. *Acta Patho Jpn* 1987;37:1389-404.
12. Furuta T, Kanematsu T, Matsumata T, Shirabe K, Yamagata M. Lipiodolization prolongs survival rates in postoperative patients with a recurrent hepatocellular carcinoma. *Hepatology* 1990;37:494-7.