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Appraisal of Surgical Treatment for Pulmonary Metastasis from Hepatocellular Carcinoma

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Abstract. The outcome of pulmonary metastasectomy of hepatocellular carcinoma (HCC) was appraised in this study. Twenty patients with pulmonary metastasis from HCCs undergoing pulmonary resection between 1990 and 2003 were included in this study. They had undergone curative treatment for the primary lesion and were candidates for a pulmonary metastasectomy for complete resection. Among the 20 patients, 13 died: 5 from hepatic failure, 5 from respiratory failure, and 2 from brain metastasis due to recurrence of the HCC. One patient died from cardiac failure without HCC recurrence. At the latest observation, three of the seven survivors were doing well without HCC recurrence, and others survived with recurrence. The overall survival rates after the initial lung surgery were 45.3% at 1 year and 23.8% at 3 years, respectively. The survival rates without recurrence were 32.4% at 1 year and 21.6% at 3 years, respectively. A Kaplan-Meier analysis showed that multiple lung surgeries and a negative histologic finding of the liver cut surface were favorable characteristics for survival without recurrence. In conclusion, the selected patients were Candidates for pulmonary metastasectomy after a curative hepatectomy for HCC and could benefit from the complete resection. Also, repeated pulmonary resections through thoracoscopy could result in the long-term survival of patients with pulmonary recurrence of HCC.

A pulmonary metastasis from malignant neoplasms is difficult to remove as a curative treatment. Metastasectomy has been thought be the choice of therapy for selected patients with a pulmonary metastasis from malignant neoplasms. Surgical treatment of the pulmonary metastasis from hepatocellular carcinoma (HCC) has been little documented to date. We therefore conducted a retrospective study on the surgical treatment of pulmonary metastasis of the HCC in our institution.

Patients and Methods

We retrospectively assessed patients who underwent an initial surgical resection of pulmonary metastasis from an HCC between 1990 and 2003 at our institution. The observation period was terminated on January 31, 2004. Patients for whom surgical resection was indicated were those who had respectable pulmonary metastases without uncontrollable tumor foci in the primary region or other organs at the time of the lung surgery and who were in a reasonably good general physical condition for the pulmonary resection.

The surgical treatment for the pulmonary metastasis was performed under general anesthesia and with controlled ventilatory support. The metastatic foci were approached either through an open thoracotomy or thoracoscopy. The metastatic tumor was resected by a pulmonary wedge resection, segmentectomy, or lobectomy. Generally, the wedge resection was performed when the pulmonary metastasis was located in the periphery of the lung. The segmentectomy or lobectomy was performed when the metastatic lesion was located deep in the pulmonary parenchyma.

Adjuvant chemotherapy was not applied postoperatively with one exception:a patient who had taken oral 5-fluorouracil after the operation. After the pulmonary metastasectomy, patients were observed at an outpatient clinic every 3 months.

The clinical characteristics assessed in each of the patients were gender, the presence of the hepatitis virus and liver cirrhosis, the maximum diameter of the primary HCC, the T factor of the HCC (UICC), the degree of differentiation of the HCC, the presence of cancer invasion into the lymphatics or vasculature, the cut-end of the liver specimen positive or negative for cancer, and the serum α-fetoprotein (AFP) level before liver surgery (an extension of the hepatectomy).

As for the pulmonary factors, a disease-free interval (DFI) (i.e., the interval between the time of the primary liver surgery and the time of the diagnosis of pulmonary metastasis), age at pulmonary metastasectomy, the number of pulmonary metastases, the location of the metastasis (peripheral or hilar region of the lung), the maximum diameter of the pulmonary metastasis, the extent of the pulmonary resection (lobectomy-segmentectomy versus wedge resection), the number of pulmonary operation, and open thoracotomy or thoracoscopy were assessed.

The surgical outcome was evaluated by the overall survival time after the initial pulmonary surgery and the survival time without

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Table 1. Clinical and pathologic characteristics of the primary lesion in the patients of this study. AFP: serum titer of α-fetoprotein (ng/ml); HBV: hepatitis B virus; HCV: hepatitis C virus.

	No. or measurement result
Gender	
Male	13
Female	7
Hepatitis virus	
HBV	10
HCV	8
Nonviral	2
Liver cirrhosis	
Yes	11
No	9
Maximum diameter of HCC (mm)	
Range	8–220
Mean ± SD	74.2 ± 54.6
T factor	
T2	1
T3	9
T4	9
Unknown	1
Degree of differentiation	
Well	1
Moderate	2
Poor	4
Unknown	13
Vascular or lymphatic involvement	
Yes	13
No	5
Unknown	2
Exposure of cancer at cut-end	
Yes	8
No	10
Unknown	2
AFP before surgery	
Range	9–199,690
Mean ± SD	17,640 ± 47,134
Treatment for primary lesion	
Surgery	19
Radio frequency ablation	1
Extent of hepatic resection	
Partial	13
Segmentectomy or lobectomy	6
History of local recurrence	
Yes	12
No	8

AFP: serum titer of α-fetoprotein (ng/ml); HBV: hepatitis B virus; HCV: hepatitis C virus.

HCC recurrence. The survival time without recurrence was defined as the interval between the time of the surgery and the latest period when the patient is/was alive without HCC.

The Kaplan-Meier method was used to estimate the survival probabilities. The curves of the two groups were compared statistically using the log-rank test. The data were considered significant when the $p < 0.05$. The statistical study was performed with the Statview statistical software package.

Results

From February 1990 to August 2003 a total of 20 patients with pulmonary metastasis from an HCC underwent surgical treatment in our department. No surgery-related deaths or major complications were observed in these patients. The mean ± SD observation time after the pulmonary surgery was 20.7 ± 21.7 months (range 3.3–81.6 months). Of the 20 patients 13 died during the observation period: 5 from hepatic failure, 5 from respiratory failure, and 2 from a brain metastasis due to HCC recurrence. One patient died from congestive heart failure without HCC recurrence. During the latest period of observation, three of the seven survivors were doing well without HCC recurrence, and the others survived despite recurrence.

The serum titer of the hepatitis B antigen tested positive in 10 patients, and that of the hepatitis C antibody was positive in 8. Eleven patients suffered from liver cirrhosis at the time of hepatectomy. The maximum diameter of the primary HCC focus was 74.2 ± 54.6 mm (mean ± SD), with a range of 8 to 220 mm. Direct invasion of the vessels or lymphatics in the primary HCC focus was found in 13 patients (negative in 5 patients, unknown in 2 patients). The T factor, according to UICC classification, was T2 in 1 patient, T3 in 9, and T4 in 9 (unknown in 1).

The histologic degree of differentiation in the HCC was well differentiated in 1 patient, moderately differentiated in 2, and poorly differentiated in 4 (unknown in 13). The serum AFH liter before liver surgery ranged from 9 to 199,690 ng/ml. The primary lesion of the HCC was resected by partial hepatectomy in 13 patients and by segementectomy or lobectomy in 6 patients. One patient did not undergo hepatectomy and, instead, had radioablation, resulting in complete remission of the primary focus. The cut-end surface of the liver specimen was positive for cancer in 8 patients and negative in 10 patients (unknown in 2 patients). Twelve patients experienced an intrahepatic recurrence (Table 1).

The DFI ranged from 0 to 27 months (mean ± SD, 13.2 ± 8.3). All patients had either solitary or multiple well demarcated nodules in the lung parenchyma. The mean ± SD age at the time of the initial lung surgery 13.2 ± 8.3 (range, 26–74 years). The mean ± SD number of the pulmonary metastasis at the initial surgery was 1.8 ± 1.6 (range, 1–8). A solitary pulmonary metastasis was found in 13 patients and multiple metastases in 7 patients. Eighteen patients had pulmonary metastases in the periphery of the lung parenchyma. We performed a wedge resection in 16 patients during the initial lung surgery, segmentectomy in 2, and lobectomy in 2. Of the 16 patients with a wedge resection, 10 underwent surgery via thoracoscopy.

Six patients underwent reresection of the pulmonary metastasis. The pulmonary surgeries were performed twice in three patients, three times in one patient, and four times in another. The reresection was performed via thoracoscopy (Table 2).

The overall survival rate after the initial lung surgery was 45.3% at 1 year and 23.8% at 3 years. The survival rate without HCC recurrence was 32.4% at 1 year and 21.6% at 3 years (Fig. 1).

The univariate analysis by the Kaplan-Meier method demonstrated that there were no significant clinical or pathologic factors influencing survival length after the pulmonary surgery, except evidence of a pathologically positive cut-end of the resected liver and the number of pulmonary surgeries. Multiple lung surgeries and a negative histologic study of the liver cut-surface were favorable characteristics for survival without the HCC recurrence (Table 3).

Discussion

The incidence of HCC is higher Japan and East Asia than in Western countries because of the prevalence of viral hepatitis.

Table 2. Clinical and pathologic characteristics of pulmonary metastases from hepatocellular carcinoma.

Characteristic	No. or measurement result
Disease-free interval (months)	
Range	0–27
Mean ± SD	13.2 ± 8.3 months
Age at pulmonary resection (years)	
Range	26–74
Mean ± SD	55.7 ± 13.4
No. of metastases	
Solitary	13
Multiple	7
Involvement of both lungs	
Yes	4
No	16
Location of pulmonary metastasis	
Peripherel	18
Hilar	2
Maximum diameter of pulmonary metastasis (mm)	
Range	7–38
Mean ± SD	19.9 ± 10.4
Extent of pulmonary resection[a]	
Partial	16
Segmentectomy or lobectomy	4
No. of pulmonary operations	
One	14
Two	4
Three	1
Four	1
Status at the last observation period	
Alive without cancer	4
Alive with cancer	3
Dead by cancer	12
Dead by other cause	1

[a]Ten patients underwent open thoracotomy; ten patients underwent thoracoscopic surgery.

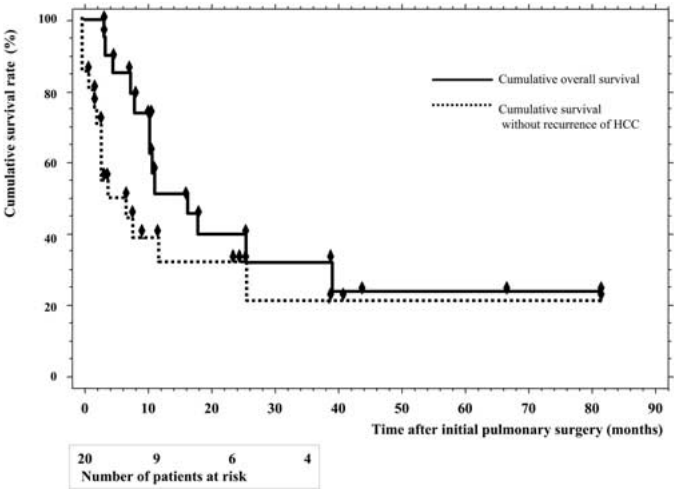

Fig. 1. Cumulative overall survival rate and the survival rate without a recurrence of hepatoceullar carcinoma (HCC).

HCC was the third most commons cause of neoplasm-related death in men and the fourth highest in women in Japan [1]. Hepatectomy ensures complete cure of the HCC; however, HCC patients with an extrahepatic metastasis are deemed unable to survive. Recently, local control of HCCs has been undertaken more properly and safely, although the number of deaths due to respiratory failure because of pulmonary metastasis has been increasing [2].

Table 3. Probability data from the log-rank test (Kaplan-Meier method) for cumulative overall survival and the survival without recurrence of HCC after the initial pulmonary surgery.

Parameter	Significance (p) Cumulative overall survival rate	Cumulative survival rate without HCC
Male vs. female	0.80	0.60
Age at lung surgery > 55 years	0.18	0.45
Viral hepatitis	0.65	0.89
Liver cirrhosis	0.14	0.18
Vascular involvement	0.13	0.46
Liver cut-end involvement	0.27	**0.011**
AFP ≥ 100 ng/ml	0.94	0.56
DFK < 12 months	0.11	0.25
Multiple pulmonary metastases	0.43	0.88
Diameter > 20 mm	0.90	0.80
Single pulmonary surgery	0.13	**0.028**
Thoracoscopy vs. open thoracotomy	0.41	0.26

Boldface indicates favorable characteristics for the survival rate without HCC recurrence.

The goal for resection of pulmonary metastases is ideally cure of the disease, but it is in fact an increased disease-free interval. Thomford et al. reported their experience with surgical resection of pulmonary metastases from various malignancies [3]. They noted that pulmonary metastasectomy was feasible when the primary lesion did not recur, if no other distant metastatic disease was present except in the lung, and the patient could tolerate complete resection. Since that time, however, surgical indications for pulmonary metastasis have been extended to multiple metastasectomy, even with liver metastasis.

Pastorino et al. reported the surgical outcome of metastasectomy from a retrospective analysis of 5206 cases with miscellaneous neoplasms from multiinstitutional data. They reported that the cumulative survival rate among 4572 cases with complete resection of pulmonary metastases was 36% at 5 years and 26% is 10 years [4]. Colorectal cancer is the most common neoplasm with pulmonary metastasis subjected to surgical treatment. The cumulative 5-year survival rates after pulmonary metastasectomy for colorectal cancer were reported to be 38% [5], 39% [6], 40% [7] and 42% [8]. These results justified surgical therapy of pulmonary metastasis, which had until then been considered representative of far-advanced and systemic neoplastic disease.

Advanced HCC metastasizes to the lung more frequently than to other organs. Tsai et al. reported 439 consecutive patients with HCC. They found that 50 of the patients had pulmonary metastases, and 10 had bone metastases. Most pulmonary metastases of HCC are found as a nodular shadow in the lung field on the chest roentgenogram or a computed tomography scan [9[. Katyal et al. conducted a retrospective study on 403 patients with HCC. They found that 148 of the patients had extrapulmonary metastasis, and these patients 81 had pulmonary metastasis [10]. Lam et al. also reported that pulmonary metastasis was observed most frequently in patients with advanced HCC [11].

Surgical treatment has been attempted for pulmonary metastasis of HCC. Lo et al. analyzed 36 patients with HCC extrahepatic metastasis. The 12 patients who underwent surgical resection for extrahepatic metastasis showed a longer survival than the other 24 patients who had been treated conservatively.

They suggested the feasibility of surgical treatment for pulmonary or bone metastases of HCC [12].

In our institution, no fewer than 600 hepatectomies for HCC were performed during the period concerned, and many of the selected patients with pulmonary metastasis of HCC were eligible for pulmonary resection [13]. The cumulative survival rates of patients with HCC undergoing a pulmonary metastasectomy were 45.3% at 1 year and 23.8% at 3 years after the lung surgery. The survival rates in this study were relatively lower than those in other reports, which might be attributed to the malignant characteristics of HCC and the difficulty with local control of HCCs postoperatively. Five patients died from hepatic failure and two from brain metastasis in the series reported herein.

We also had six patients who underwent a second surgery for recurrent pulmonary metastasis. All of the pulmonary reresections were performed via thoracoscopy, and the surgical outcome of the patients with multiple pulmonary resections was significantly better than those with a single pulmonary metastasectomy. Jacklitsch et al. analyzed the prognosis of the patients with multiple pulmonary metastasectomies and concluded that multiple attempts to reestablish intrathoracic control of the metastatic disease were justified in carefully selected patients [14]. We adapted thoracoscopy for remetastasectomy to treat pulmonary recurrence of HCC successfully. We suggest that thoracoscopy is feasible for accomplishing multiple surgeries to remove pulmonary metastases with less invasiveness.

Conclusions

We concluded that it is feasible in selected patients to perform pulmonary metastasectomy after a curative hepatectomy for HCC, and such patients can benefit from an active surgical approach to remove the metastatic foci completely. We also concluded that a repeat pulmonary resection via thoracoscopy for an HCC metastasis could result in the long-term survival of patients with a pulmonary recurrence.

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