European Journal of Cardio-Thoracic Surgery 41 (2012) 376–382
doi:10.1016/j.ejcts.2011.05.052

ORIGINAL ARTICLE

Outcome and survival analysis of pulmonary metastasectomy for hepatocellular carcinoma

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Received 18 March 2011; received in revised form 18 May 2011; accepted 25 May 2011

Abstract

OBJECTIVE: The lung is the most common site for extrahepatic metastasis from hepatocellular carcinoma (HCC). We previously reported in a series of 20 patients that pulmonary metastasectomy for HCC is feasible in selected patients. The objective of this study was to re-evaluate the long-term outcomes and prognostic factors with an additional 25 patients.

METHODS: We retrospectively analyzed the records of 45 consecutive patients who underwent pulmonary metastasectomy due to HCC at our institution between 1990 and 2010.

RESULTS: Thirty-nine patients underwent hepatectomy or liver transplantation, whereas six patients underwent locoregional therapy for primary liver lesions. Twenty-seven patients died during a median 17.6-month follow-up period. The 2-year disease-free survival (DFS) was 19.5%. The 5-year overall survival (OS) was 40.9%. History of recurrence and serum des-gamma-carboxy prothrombin (DCP) level >40 mAU ml^{-1} at initial pulmonary resection were unfavorably associated with OS in univariate analysis.

CONCLUSIONS: Pulmonary metastasectomy for HCC in selected patients resulted in relatively good outcomes with regard to OS. History of recurrence and serum DCP levels were shown to be candidates of prognostic factors for OS.

Keywords: Metastases/metastasectomy (hepatocellular carcinoma, lung) • Statistics • Survival analysis

INTRODUCTION

Hepatocellular carcinoma (HCC) is a highly aggressive cancer with a high mortality rate. Although recent advancements in intrahepatic treatment modalities have improved the prognosis for HCC, the prognosis of patients with extrahepatic metastases remains poor. The lung is the most common site of extrahepatic metastasis [1]. We previously reported in a series of 20 patients that selected patients can be candidates for resection of pulmonary metastases from HCC [2]. There have been a few studies of pulmonary metastasectomy for HCC; however, the associated prognostic factors have not been well established until now. The objective of the current study was to present our experience with pulmonary metastasectomy for HCC with an additional 25 patients and to re-evaluate the prognostic factors.

PATIENTS AND METHODS

We retrospectively reviewed the records of 45 consecutive patients who underwent an initial pulmonary metastasectomy for HCC at our institution between 1990 and 2010. The observation period was terminated on 31 January 2011.

Our selection criteria for metastasectomy for HCC were as follows: (1) possibility of complete resection, (2) no evidence of uncontrolled intrahepatic or extrapulmonary lesions at the time of the lung surgery, and (3) adequate general physical condition for the pulmonary resection. Synchronous pulmonary metastases with primary or recurrent HCC were not considered as a contraindication if the hepatic lesion was thought to be controllable. In such cases, a single operation was performed for resection of hepatic and pulmonary lesions.

Pulmonary metastasectomy was performed under general anesthesia and with controlled ventilatory support in all cases. The metastatic lesions were approached either via an open thoracotomy or via thoracoscopy. In most of the cases, wedge resection was performed and, if needed for complete resection, segmentectomy or lobectomy was performed. After pulmonary metastasectomy, patients were followed up at regular intervals of 1-3 months by physical examination, chest radiography, evaluation of serum tumor markers, such as alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), ultrasonography of the liver, and computed tomography (CT) of the lung and abdomen.

We recorded patient-related characteristics (age, sex, smoking history, history of coronary artery disease, diabetes mellitus, and malignant diseases other than HCC), variables at initial treatment

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for primary HCC (presence of viral hepatitis, liver cirrhosis, Child–Pugh class, and tumor stage according to the seventh edition of the American Joint Committee on Cancer staging manual), and variables at initial pulmonary metastasectomy (tumor markers, number of metastatic nodules, laterality, maximum size of the metastatic nodules, extent of resection, and method of approach). Any history of recurrence before detection of the initial pulmonary metastasis and treatments adopted before and after the initial pulmonary metastasectomy were also recorded. Locoregional therapy for liver lesions included percutaneous ethanol injection, radio frequency ablation, and transcatheter therapies, such as arterial embolization or chemoembolization. We counted planned two-stage procedures for bilateral pulmonary metastases as a single operation. Disease-free interval (DFI) was defined as the time between the day of extirpation of primary HCC or last recurrent tumor, if any, and the day of detection of the first pulmonary metastatic nodules. The liver-to-lung interval was defined as the time between the day of the initial treatment for HCC and the day of detection of the first pulmonary metastatic nodules. Primary outcomes were overall survival (OS) and disease-free survival (DFS) from the times of initial pulmonary metastasectomy. DFS was defined as the time from initial pulmonary metastasectomy to the day when intrahepatic or any extrahepatic recurrence was detected or the patient died. We also recorded the cause of death. Before the study, the Research Review Board at our institution examined and approved our research protocol in accordance with the Declaration of Helsinki. All patients provided written informed consent before surgery.

Relationships between clinical variables were assessed with the chi-square test, the Wilcoxon test, and Fisher's exact test, as appropriate. Survival times were calculated using the Kaplan–Meier method, and univariate analysis was performed using the

Table 1: Characteristics of 45 patients undergoing pulmonary metastasectomy for hepatocellular carcinoma

Characteristic	No. or measurement results
Patient-related characteristics	
Age (years) (median (range))	57 (26–80)
Sex (male/female)	33/12
Smoking history (current or former smoker/never smoker)	25/20
Diabetes mellitus (present/absent)	7/38
Coronary artery disease (present/absent)	1/44
Malignancies other than HCC[a] (yes/no)	4/41
Variables at initial treatment for primary hepatocellular carcinoma	
Viral hepatitis (type B/type C/nonviral)	21/17/8
Liver cirrhosis (present/absent)	18/25
Child–Pugh class (A/B/C/unknown)	34/5/0/6
Tumor stage (I/II/IIIA/IIIB/IIIC/IVB)	11/9/10/5/6/4
Variables at initial pulmonary metastasectomy	
Disease-free interval (months) (median (range) [25, 75 percentile])	7.6 (0–104.3) [3.9, 16.2]
Liver-to-lung interval (months) (median (range) [25, 75 percentile])	14.3 (0–107.2) [8.9, 30.7]
AFP (ng ml^{-1}) (median [25, 75 percentile])	45 [5, 267]
Serum DCP (mAU ml^{-1}) (median [25, 75 percentile])	89 [23, 240]
Child–Pugh class (A/B/C)	43/2/0
Number of metastatic nodules (one/two/three or more)	26/9/10
Laterality (unilateral/bilateral)	34/11
Maximum size of the metastatic nodules (mm) (median (range))	17 (2–70)
Extent of pulmonary resection (wedge resection/segmentectomy or lobectomy)	37/8
Approach method (open thoracotomy/thoracoscopic)	14/31

HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin.
[a] Malignancies include two resected cases of synchronous stage IA primary lung cancer, one resected case of synchronous stage IB gastric cancer, and one history of eradicated cervical lymph node squamous cell carcinoma of unknown origin.

Table 2: Treatment modalities adopted before and after initial pulmonary metastasectomy

Treatment modality	No. of patients receiving treatment before initial pulmonary metastasectomy	No. of patients receiving treatment after initial pulmonary metastasectomy
Hepatectomy (repeated)	37 (7)	7 (3)
Liver transplantation	3	0
Percutaneous injection or ablation (repeated)	11 (7)	5 (1)
Transcatheter therapy (repeated)	32 (17)	14 (8)
Systemic chemotherapy	5	13
Molecular targeting therapy	0	3
Extrapulmonary metastasectomy (repeated)	5	5 (2)
Repeated pulmonary metastasectomy (1/2/4/6 times)	–	9/2/1/1

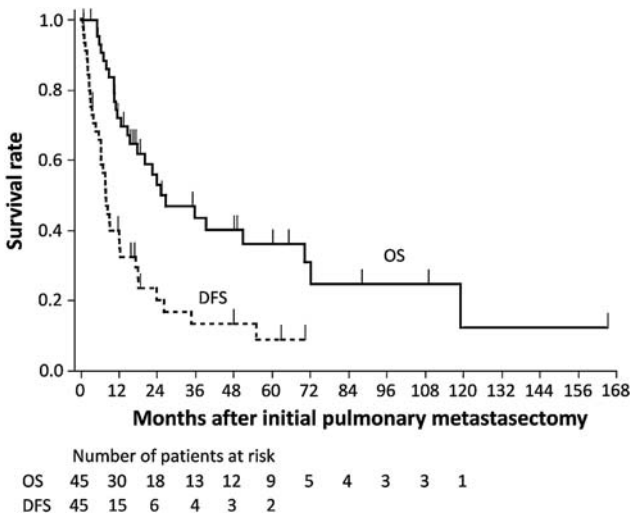

Figure 1: Survival curves generated by the Kaplan–Meier method. DFS: disease-free survival; OS: overall survival.

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log-rank test. A P value of less than 0.05 was considered significant. Statistical analysis was performed with JMP 7 software (SAS Institute, Cary, NC, USA).

RESULTS

Among the 45 patients, 33 were men. The median age at initial pulmonary metastasectomy was 57 (range 26–80) years. A wide range of tumor stage of the primary HCC was included, varying from stage I to stage IVB (Table 1). In one patient, right adrenal gland metastasis was detected at initial diagnosis of primary HCC, which was concomitantly resected with the hepatoma. Thirty-nine patients underwent hepatectomy and/or liver transplantation, whereas six patients underwent locoregional therapy for primary liver lesions.

The median DFI was 7.6 (range 0–104.3) months, and the median liver-to-lung interval was 14.3 (range 0–107.2) months.

Table 3: Survival and univariate analysis according to clinical variables

Variables	No. of patients	Disease-free survival			Overall survival		
		1 year (%)	2 years (%)	*P* value	2 years (%)	5 years (%)	*P* value
Age at initial pulmonary metastasectomy (years)							
< 55	18	33.3	20.8	0.8398	43.2	23.1	0.3439
≥ 55	27	40.3	17.9		61.3	48.2	
Sex							
Male	33	42.3	23.4	0.2337	49.3	33.1	0.2839
Female	12	25.0	–		66.6	50.0	
Viral hepatitis							
Present	37	33.1	15.5	0.1067	49.2	33.5	0.4953
Absent	8	58.3	43.7		71.4	47.6	
Liver cirrhosis							
Present	18	27.7	20.8	0.3661	46.3	26.4	0.2083
Absent	25	43.8	23.3		62.9	48.9	
Tumor stage							
I or II	20	50.0	27.7	0.1374	69.6	52.2	0.1637
IIIA, IIIB, IIIC, or IVB	25	26.5	13.2		43.4	27.9	
Treatment for primary HCC							
Hepatectomy and/or liver transplantation	39	35.4	20.5	0.8855	57.8	39.5	0.1641
Locoregional therapy	6	50.0	0		0	–	
Disease-free interval (months)							
< 12	30	32.8	15.6	0.1106	47.3	27.9	0.2203
≥ 12	15	45.7	28.5		64.1	53.4	
Liver-to-lung interval (months)							
< 12	19	36.3	22.7	0.7931	60.8	43.4	0.3297
≥ 12	26	38.0	19.3		47.6	32.1	
AFP (ng ml^{-1})							
≤ 100	28	34.9	18.3	0.6909	56.9	31.5	0.7123
> 100	17	41.1	23.5		46.3	39.7	
DCP (mAU ml^{-1})							
≤ 40	18	55.0	28.5	0.0443	68.1	47.4	0.0394
> 40	27	24.4	14.6		42.5	27.5	
History of recurrence							
Absent	24	45.9	35.0	0.0554	70.1	63.1	0.0028
Present	21	28.5	5.9		35.7	8.9	
Number of metastatic nodules							
Solitary	26	42.3	24.0	0.6267	56.1	49.9	0.8219
Multiple	19	28.9	14.4		49.2	21.1	
Laterality							
Unilateral	34	39.4	20.0	0.9055	59.3	41.8	0.9458
Bilateral	11	31.8	21.2		36.0	24.0	
Maximum size of the metastatic nodules (mm)							
≤ 15	20	42.6	21.3	0.4183	59.9	43.7	0.4879
> 15	25	32.8	18.7		47.8	31.9	
Extent of pulmonary resection							
Wedge resection	37	39.0	22.0	0.5381	55.6	35.3	0.9023
Segmentectomy or lobectomy	8	28.5	–		38.1	38.1	
Approach method							
Open thoracotomy	14	15.3	–	0.0042	30.7	30.7	0.3266
Thoracoscopy	31	46.9	29.7		62.7	37.4	
Number of pulmonary surgeries							
Single	32				42.3	37.0	0.1965
Multiple	13				76.1	42.3	

AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; HCC: hepatocellular carcinoma.

Median serum levels of AFP and DCP at initial pulmonary metastasectomy were 45 (range 0.8– 8200) ng mT^{-1} and 89 (range 0–9000) mAU ml^{-1}, respectively. Of 19 patients with multiple metastatic nodules, 11 patients had bilateral metastases. Open thoracotomy was performed in 14 patients and thoracoscopy in 31.

Twenty patients developed intrahepatic recurrence before the initial detection of pulmonary metastasis. Seventeen patients underwent repeated transcatheter treatments for recurrent intrahepatic lesions before initial pulmonary metastasectomy (Table 2). Extrahepatic recurrences were detected in four patients, which were well controlled. The sites of extrahepatic recurrences included the brain, skull, left adrenal gland, and peritoneum. Taken together, a total of 21 patients had a history of intrahepatic or extrahepatic recurrence before initial pulmonary metas-tasectomy, whereas 24 patients did not. The latter group had shorter liver-to-lung intervals ($P = 0.0289$), and more advanced tumor stage of the primary HCC ($P = 0.0253$).

The median follow-up period after initial pulmonary metastasectomy was 17.6 (range 0.7–165) months. Recurrences were actively treated by various modalities (Table 2). Thirteen patients underwent a total of 23 repeated pulmonary resections for newly detected pulmonary metastases during follow-up. No hospital mortality occurred. However, in one patient, empyema due to prolonged air leakage occurred after the second pulmonary metastasectomy, which required open thoracostomy followed by thoracoplasty. No morbidity due to thoracoscopic procedures such as port site recurrences was observed.

During the follow-up, 27 of the 45 patients died. Causes of death were liver failure due to HCC progression in 15, brain metastases in 7, and respiratory failure due to pulmonary metastases in 6, with overlap. The causes of death among the other patients were heart failure in relation to polymyositis in 1, pneumonia in 1, and unknown in 1. At the end of the observation period, 14 of the 18 survivors remained free of disease. No relationships were found between clinical variables and causes of death except for DCP; compared to 20 patients who died without brain metastases, patients succumbed to brain metastases tended to have less incidence of having serum levels of DCP more than 40 mAU ml^{-1} ($P = 0.0114$).

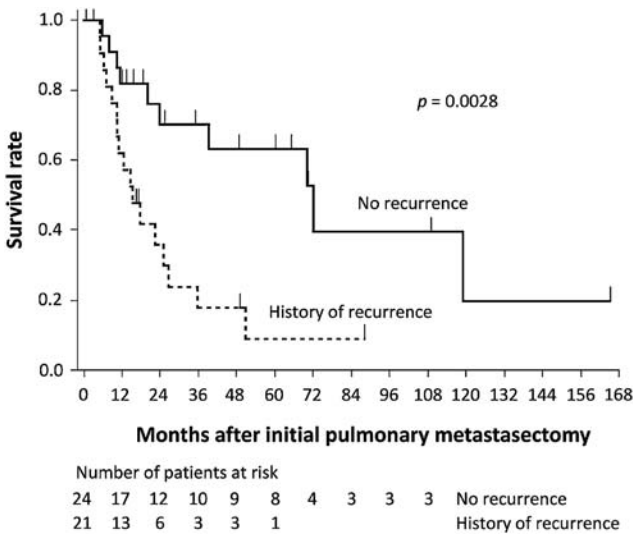

Figure 2: Overall survival according to the history of recurrence generated by the Kaplan–Meier method.

The median OS was 26.5 (range 0.7–165) months; and the actual 2- and 5-year OS rates were 53.9% and 40.9%, respectively. The median DFS was 7.7 (range 0.5–70) months; and the actual 1- and 2-year DFS rates were 36.2% and 19.5%, respectively (Fig. 1).

In univariate analysis, patients with serum levels of DCP more than 40 mAU ml^{-1} or history of recurrence were found to have poorer OS (Table 3). Survival curves according to the history of recurrence are shown in Fig. 2. No significant difference was observed between the survival of patients who were enrolled in our previous study and those who were not ($P = 0.1021$). In terms of DFS, serum levels of DCP more than 40 mAU ml^{-1} or open thoracotomy were poor prognostic factors (Table 3).

DISCUSSION

HCC is still one of the most common cancers and causes of cancer death worldwide. Advancements in therapeutic modalities, such as surgical resection, radio frequency ablation, percutaneous ethanol injection, and transcatheter arterial chemoembolization, have gradually improved the prognosis of patients with HCC. Nevertheless, the prognosis of patients with extrahepatic metastases remains poor. In two studies, the median survival time was less than 7 months and the 1-year survival rate was as low as 25% [1,3].

Indications for pulmonary metastasectomy can differ among various types of malignancies. In general, resection of pulmonary metastases is not indicated if any recurrent foci are recognized at the primary site. In the case of HCC, however, intrahepatic recurrences often occur but are regarded to be well controllable by re-resections or other local treatments. In this series, we included patients with a history of intrahepatic or extrapulmonary recurrences as candidates for pulmonary metastasectomy as long as the recurrent tumors were well controlled.

Resection of pulmonary lesions also offers diagnostic benefits for patients with treated HCC [4]. Pulmonary lesions in at least seven patients with history of HCC were resected at our institute during the period concerned and were diagnosed as primary lung cancers. These patients were excluded from the current study. In the current series of patients who underwent pulmonary metastasectomy, two patients had synchronous occult stage IA primary lung cancers, which were concomitantly resected.

In our present study, the median OS after pulmonary metastasectomy was 26.5 months, the 5-year OS was 36.2%, the median DFS was 7.7 months, and the 2-year DFS was 20.2%. Our 5-year survival rate is similar to that reported by Nakagawaetal. (36%) [5] andYoon et al. (37.0%) [6]. It seems to be a consistent result that the DFS time is relatively short compared to the OS time. We believe that the aggressive treatment for recurrent tumors including repeated pulmonry metastasectomy has contributed in some part to the “elatively long OS.

Several studies of pulmonary metastasectomy for HCC lave been conducted previously (Table 4). Among those in which 20 or more patients enrolled, DFI before pulmonary metastasectomy [5–7], AFP [5,7], number of metastatic esions [6,8,9], hepatic margin [2,7], and hepatectomy as a reatment for primary HCC [9] were reported as candidates Or preoperative prognostic factors.

DFI has been accepted as a prognostic factor for pulmonary metastasectomy in various malignancies [10]. A horter DFI may

Table 4: Summary of previously reported pulmonary metastasectomy for hepatocellular carcinoma

Year	Author	Selected patients	No. of patients	Mean ± SD Follow-up (months)	Median survival (months)	Longest survival (months)	5-year OS (%)	Summary
1998	Lam et al. [13]	Post-Hx and solitary PM	9	42.6 ± 29.8	NR	101	67	Report of long-term survival in highly selected patients
2004	Gwak et al. [14]	2 post-Hx and 2 post-Lx	4	49.5 ± 15.7	NR	72	75	Report of long-term survival
2004	Chen et al. [15]	Post-Hx	6	47.2 ± 34.3	NR	94	67	Aggressive surgical resection for multiple lesions (five patients), bilateral lesions (two patients), patients with liver cirrhosis (three patients)
2005	Nakajima et al. [2]	19 post-Hx and 1 post-Lx	20[a]	20.7 ± 21.7	NR	81.6	NR	Favorable factors for HCC-free survival: negative liver cut-end involvement and multiple lung surgeries
2006	Nakagawa et al. [5]	Post-Hx	25	36.8 ± 41.2	51.8	177.4	36	Favorable factors for survival: DFI > 12 months and AFP before metastasectomy < 500 ng ml^{-1}
2006	Tomimaru et al. [16]	Post-Hx	8	28.5 ± 23.5	28	80	33	Survival of PM resection group was better than nonresection group
2007	Kuo et al. [7]	Post-Hx	34	30	NR	115	27.5	Unfavorable factors for survival: AFP ≥ 100 ng ml^{-1}, hepatic margin <1 cm, and DFI <12 months
2007	Koide et al. [17]	Post-Hx	14	21.6 ± 17	21.6	66	26.8	Favorable factor for survival: no history of TAE
2008	Kawamura et al. [8]	Post-Hx	61[b]	NR	NR	NR	32.2	In multivariate analysis: survival of patients with number of lesions ≤ 2 was better than patients with three or more lesions
2008	Chen et al. [18]	10 post-Hx and 2 post-Tx	12	20 (median)	NR (33)	79	28.9	Favorable factor for survival: maximum PM size < 3 cm
2008	Kwon et al. [19]	5 post-Hx, 7 post-Tx, and 5 post-Lx	16	26.7 ± 28.2	20	98	26	Favorable factors for survival: Tx, good differentiation of HCC, and negative HBV infection
2008	Bates et al. [20]	Post-Tx	5	44.4 ± 22.3	NR	80	Unreached	Survival times of Tx patients with PM are similar to those of Hx patients with PM
2010	Lee et al. [9]	21 post-Hx, 1 post-Tx, and 10 post-Lx	32	20.7 ± 26.1	10.7	97.6	NR	Favorable factors in multivariate analysis: HCC controlled by surgery and number of lesions ≤ 2
2010	Han et al. [21]	28 post-Hx, 12 post-Tx, and 1 post-Lx	41	25 (median)	77	137	66.9	Unfavorable factors for survival in multivariate analysis: presence of extrahepatic/extrapulmonary recurrence after pulmonary metastasectomy
2010	Yoon et al. [6]	Post-Hx	45	16.3 (median)	40.7	118.8	37	Favorable factors for survival: first recurrence in lung, long DFI, and solitary PM
2010	Cho et al. [22]	Post-Hx	17	28.9 (median)	28.9	78.5	11.8	Favorable factors for survival: AFP after metastasectomy < 100 ng ml^{-1} and DFI > 24 months
2011	Our study	39 post-Hx, 3 post-Tx, and 6 post-Lx	45	32.8 ± 34.9	26.5	165.3	38	Unfavorable factors in multivariate analysis: history of recurrence and DCP > 40 mAU ml^{-1}

AFP: alpha-fetoprotein; DCP: des-gamma-carboxy prothrombin; DFI: disease-free interval; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; Hx: hepatectomy; Lx: locoregional therapy; NR: not reported; OS: overall survival; PM: pulmonary metastasis; TAE: transarterial chemoembolization; Tx: liver transplantation.

[a] All 20 patients were included in our study.

[b] 21 out of 61 patients were included in our study.

indicate a more aggressive biology of the primary tumor and ultimately result in poorer OS. Because our series included patients with and without a history of recurrence, we recorded two variables with respect to time intervals that may reflect tumor aggressiveness: the liver-to-lung interval and DFI. The liver-to-lung interval, which started from the day of initial treatment for HCC, may indicate the progress of the entire HCC course. DFI, started from the day when the last treatment for HCC was completed, was thought to reflect the aggressiveness of the latest appearing tumor foci. In our series, however, neither DFI nor liver-to-lung interval was significant prognostic factors.

Yoon et al. showed that first recurrence in lung rather than in liver was a good prognostic factor [6]. Similarly in our study, the absence of a history of recurrence was a good prognostic factor. Our patient inclusion criteria differed from those of Yoon et al. in the following aspects. First, the initial treatment for primary HCC was not restricted to hepatectomy. Second, patients with primary HCC and synchronous metastases were included. Third, patients with a history of controlled recurrence other than liver or lung were also included. In the case of pulmonary metastasis without a history of recurrence, pulmonary lesions presumably metastasized directly from the primary HCC but were undetectable macroscopically at the time of the treatment of the primary site. By contrast, the metastatic origin of pulmonary lesions found in patients with a history of controlled recurrence should have been the recurrent liver foci, at least in some cases. In such cases, the liver-to-lung interval would be relatively longer because it includes the period in which primary lesion was well controlled, although it does not indicate that the nature of the metastatic tumors is less aggressive. Moreover, a shorter liver-to-lung interval may represent a bias resulting from an earlier timing of intervention in the entire HCC course. A history of recurrence may thus be a discernible and consistent parameter that implies the prognosis of patients with pulmonary metastases from HCC. Patients with a history of recurrence might not benefit from undergoing pulmonary metastasectomy, even if the recurrence seemed to have been well controlled.

DCP, also known as protein induced by vitamin K absence or antagonist II, has been reported as a prognostic marker in HCC [11]. To our knowledge, however, no previous studies of pulmonary metastasectomy have mentioned DCP as a preoperative prognostic factor. In our series, patients with levels of serum DCP of more than 40 mAU ml^{-1} at initial pulmonary metastasectomy had significantly poorer OS. DCP may be a simple parameter in selecting patients for pulmonary metastasectomy. Another common tumor marker, AFP, was not a significant prognostic factor in our study.

Patients who underwent thoracoscopic surgery at initial pulmonary surgery had a longer DFS but had no significant difference in OS. We did not determine clinical factors that may have influenced the choice of approach. On the basis of our previous work [12], we believe that bimanual palpation of the whole lung through open thoracotomy is not mandatory because small metastatic nodules are often missed regardless of the method of approach into the thorax. Given the high incidence of repeated pulmonary metastasectomy, we stress that thoracoscopy is feasible and less invasive for multiple pulmonary surgeries.

The present study has several limitations. First, the tumor stage of the primary HCC, which should influence the survival, was not stratified because of the insufficient number of patients enrolled. Second, treatment modalities for primary HCC were heterogeneous owing to the recent development of treatment modalities and strategies. Third, patients in our series were highly selected. Patients with lethal episodes of recurrence were excluded from the study, which led to overestimation of the outcome of the survivors. Thus, the 45 patients in the study would not represent a general population of patients with pulmonary metastasis from HCC.

In conclusion, pulmonary metastasectomy in selected patients with HCC resulted in a relatively good outcome with regard to OS. The DFS time after initial pulmonary metastasectomy was relatively short compared to the OS time. A history of recurrence and serum levels of DCP were found to be prognostic factors associated with OS and DFS in univariate analysis. These factors should be taken into account when considering pulmonary metastasectomy for HCC.

ACKNOWLEDGMENTS

We thank Norihiro Kokudo and Kiyoshi Hasegawa at the Division of Hepato-Biliary-Pancreatic and Transplantation Surgery, University of Tokyo, who provided insight and expertise that greatly assisted the research.

Conflict of interest: none declared.

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