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ORIGINAL SCIENTIFIC REPORT

Prognostic Analysis of Surgical Resection for Pulmonary Metastasis from Hepatocellular Carcinoma

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Abstract

Introduction Pulmonary metastases are the most common among extrahepatic recurrences from hepatocellular carcinoma (HCC). It causes high risk of HCC-related death, despite recent progress in therapeutic options. However, a role of pulmonary metastasectomy as well as prognostic factors after metastasectomy has not been well established. We aimed to investigate survival outcomes and prognostic factors after pulmonary resection for metastases from HCC.

Methods A series of 93 patients who underwent pulmonary resections for metastases from HCC between June 1990 and July 2013 from multi-institutional database were retrospectively evaluated. Perioperative clinicopathological data and their association with prognosis were investigated.

Results Of 93 patients, 77 had one pulmonary metastasis, and 16 had two or more. Recurrence after pulmonary resection was noted in 60 patients (64.5 %). The estimated 5-year overall survival rate was 41.4 % with median survival time after pulmonary metastatectomy of 39.0 months. Univariate prognostic analysis showed that disease-free interval of $\geq$12 months was significantly associated with favorable outcomes in both overall survival (5-year rate, 59.3 vs. 28.7 %, $p = 0.026$) and disease-specific survival (5-year rate, 62.5 vs. 36.2 %; $p = 0.038$) after pulmonary metastatectomy. A multivariate analysis revealed that disease-free interval was an independent prognostic factor (HR = 2.020, 95 % CI, 1.069–3.816, $p = 0.030$).

Conclusion We have shown that a disease-free interval was an independent prognostic factor in patients who underwent pulmonary resection for metastasis from HCC. Also, pulmonary metastasectomy can be one of the therapeutic choices for select patients.

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Abbreviations

HCC	hepatocellular carcinoma
PM	pulmonary metastases
CT	computed tomography
OS	overall survival
DSS	disease-specific survival
DFI	disease-free interval
IQR	interquatile range
SD	standard deviation

Introduction

Hepatocellular carcinoma (HCC) is one of the major causes of cancer-induced death worldwide. Although recent advances in local and systemic therapeutic options for intrahepatic recurrence have resulted in improved local control rates [1, 2], the recurrence rate after local therapy reportedly still ranges from 75 to 100 % [2–4]. Thus, the long-term prognosis of HCC after local therapy remains poor [2, 5]. To improve outcomes further, more aggressive treatment of extrahepatic recurrence may be required. Pulmonary metastasis (PM) is the most common type of extrahepatic recurrence from HCC, which occurs much less frequently than intrahepatic recurrence [4]. Surgical treatment for extrahepatic recurrence is considered to be controversial to date [6]; however, recent literature suggests that pulmonary metastasectomy is an effective treatment choice in select patients [7, 8]. However, prognostic factors after pulmonary metastasectomy are currently not well understood. Our study aimed to investigate long-term survival outcomes and prognostic factors after pulmonary resection for metastasis from HCC.

Patients and methods

We established the 26-institution Metastatic Lung Tumor Study Group of Japan in 1984, and have collected clinicopathological data from patients who underwent pulmonary metastasectomy with curative intent for various malignancies. During the period from June 1990 to July 2013, a total of 3473 patients who underwent surgical resection for metastatic lung tumors were enrolled in this registry. Our inclusion criterion was all patients who underwent surgical resection for PM from HCC after complete resection for primary HCC in the institutions belonging to the consortium. Among the population, we selected the 110 patients in accordance with the inclusion criterion. Subsequently, 17 patients were excluded due to the following exclusion criteria: unavailable essential data ($n = 11$) and follow-up of <12 months ($n = 6$). Consequently, the study cohort comprised 93 (2.7 %) consecutive patients with PM from HCC who underwent surgical resection. Institutional Review Board-approved informed consent was obtained from all patients. The following clinicopathological data were recorded in the registration form: gender, date of birth, date and time of treatment for HCC, date of detection of PM, number of lesions on right and left lungs, maximum tumor diameter, date and time of resection of PM, number of resections, type of surgical procedure, and the date of last follow-up. Preoperative diagnosis of PM was made based on the computed tomography (CT) findings. Chest CT of each patient was preoperatively evaluated to assess which procedure is needed to secure sufficient surgical margins. Surgical procedure was decided in consideration of intraoperative findings exclusively by each attending surgeon. Resected specimens were pathologically assessed.

Although detailed liver function was not mandatory, the patients were required sufficient liver function and cardiopulmonary reserve for pulmonary resection. The indication of surgical resection for PM was independently determined by each institution, even though we have generally assumed the criteria proposed by Thomford et al. as a standard [9], which require that the primary malignancy to be controlled, and there are no other metastatic lesions and also sufficient general reserve of the patient for surgical resection. Patients were followed up with chest CT scan twice or thrice a year to detect the recurrence of HCC including the PM, and additional imaging studies were performed at the discretion of the treating physician, if necessary. Survival outcome surveys were subsequently conducted at 1-year intervals by the registration center.

Overall survival (OS) was measured by comparing the date of pulmonary metastasectomy to the date of death from any cause, or the date on which the patient was last known to be alive. The disease-specific survival (DSS) time was measured from the date of pulmonary metastasectomy to the date of death from HCC; the observations were censored at death from causes other than HCC; locoregional recurrences, distant metastases, and second primary cancer were ignored. Disease-free interval (DFI) was defined as the time between the day of curative surgery of intrahepatic lesion and the day of the detection of PM, giving a DFI of 0 if PM were detected prior to the initial liver resection. Survival curves were plotted, and cumulative survival rates were calculated using the Kaplan–Meier method. Comparisons were performed using the log-rank test as a univariate analysis. To determine the independent prognostic factors, a multivariate analysis was conducted using the Cox-proportional hazard model. Two-category comparisons were performed using the Pearson χ^2 test and the Fisher exact test for quantitative data. All the tests were

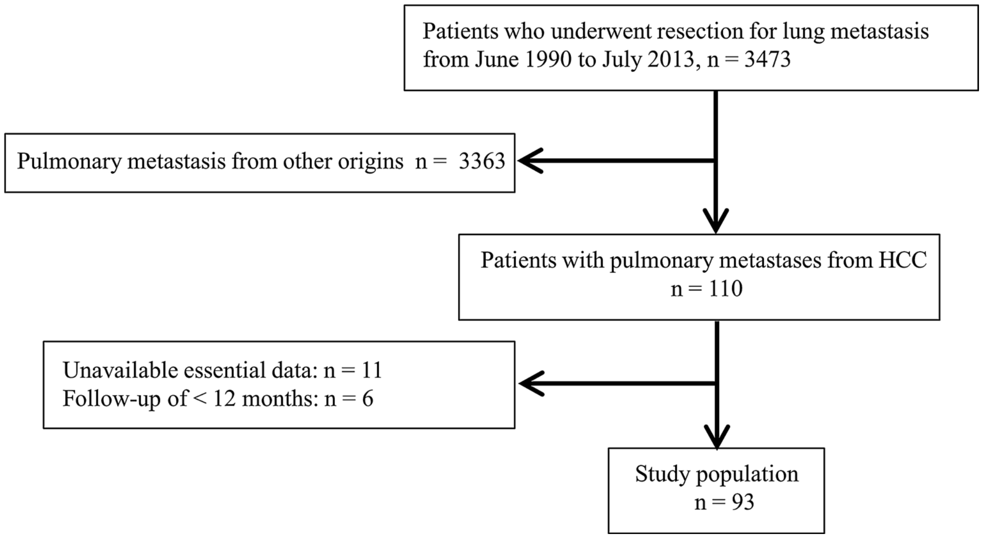

Fig. 1 Flow chart of patient selection

Table 1 Baseline characteristics of the study cohort

Median age at metastatectomy (years, IQR)	64.0 (54.5–71.0)
Gender	
Male	74
Female	19
Histological differentiation of primary HCC	
Well-to-moderate	86
Poor	7
Median follow-up period (months, IQR)	42.0 (21.5–65.0)
Median disease-free interval (months, IQR)	17.0 (7.0–29.5)
Median greatest diameter of pulmonary metastasis (mm, IQR)	18.0 (12.0–27.0)
Laterality of pulmonary metastasis	
Right	43
Left	38
Bilateral	12
Number of metastatectomy	
1	77
2	12
3	2
4	2
Extent of resection	
Wedge resection	77
Segmentectomy or lobectomy	16
Treatment for recurrence following metastasectomy	
Chemotherapy	10
Radiotherapy	3
Other ablations	11

IQR interquatile range, *CEA* carcinoembryonic antigen

two-sided, and p values less than 0.05 were considered statistically significant. The statistical analysis was performed using SPSS software (version 20; SPSS Inc., Chicago, IL).

Results

We extensively reviewed 3473 patients who underwent pulmonary metastasectomy from June 1990 to July 2013, selecting 110 patients with PM from HCC who met our inclusion criteria. Then, 11 cases were excluded due to missing essential data as well as six other cases excluded due to insufficient follow-up period less than 12 months. Finally, we employed 93 patients and performed the following analysis (Fig. 1).

Baseline characteristics of the study cohort are presented in Table 1. Median postoperative follow-up was 42.0 months (IQR 21.5–65.0). The current cohort included 74 male (79.6 %) and 19 female (20.4 %), with median age at pulmonary metastatectomy of 64.0 (IQR 54.5–71.0) years. Histological grades of primary HCC were 86 cases of well-to-moderate and seven cases of poor. Median DFI was 17.0 (IQR 7.0–295) months. Of 93 patients, 77 had one PM, 12 had two, 2 had three, 2 had four, and the mean number of PM was 1.24 ± 0.597 (mean ± SD). Median greatest diameter of PM was 18.0 (IQR 12.0–27.0) mm. 43 cases had right-side lesions, 38 had left-side lesions, and 12 had bilateral lesions. 77 (82.8 %) underwent wedge resection, and 16 (17.2 %) underwent lobectomy or segmentectomy for PM.

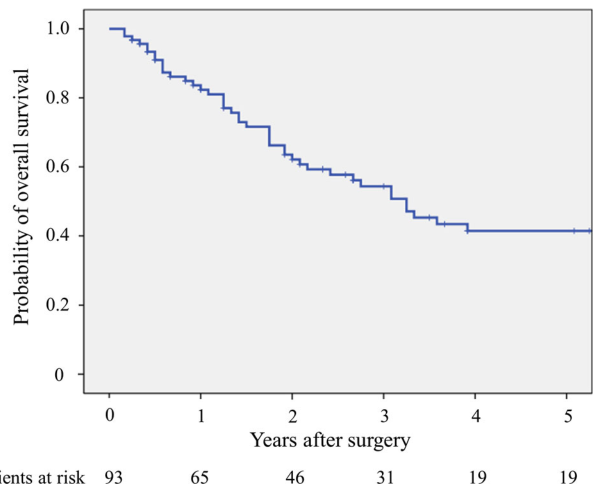

Fig. 2 Kaplan–Meier overall survival curve after resection for patients with pulmonary metastasis from hepatocellular carcinoma

Recurrence after pulmonary resection was noted in 60 patients (64.5 %) by April 2015. Disease-specific death was observed in 37 cases during the study period. The most common recurrence was intrahepatic in 52 patients, and pulmonary recurrence after pulmonary metastasectomy was detected in 2 patients (2.15 %). No repeated pulmonary resection was performed in our series. For recurrent diseases following pulmonary metastasectomy, 10 patients underwent chemotherapy, 3 patients underwent radiotherapy, and 11 patients underwent other ablations for recurrence. As shown in Fig. 2, the estimated 5-year OS rate was 41.4 %. The median OS time after pulmonary metastasectomy was 39.0 months.

To identify prognostic factors, we selected seven categorical variables: age (<65 years vs ≥65 years), gender (male vs female), DFI (<12 months vs ≥12 months), tumor laterality (unilateral vs bilateral), number of PM (solitary vs multiple), maximum tumor size (≤30 mm vs

Table 2 Univariate prognostic analysis by Kaplan–Meier methods

Factors	Patient no.	5-year survival (%)	*p* value[a]
Age (years)			
<65	47	42.8	0.900
≥65	46	40.4	
Gender			
Male	74	41.8	0.375
Female	19	41.1	
Histological grade of primary HCC			
Well to moderately differentiated	86	40.4	0.573
Poorly differentiated	7	50.0	
History of recurrence before metastasectomy			
No	69	42.6	0.930
Yes	24	41.4	
Disease-free interval			
<12 months	55	28.7	0.026
≥12 months	38	59.3	
Laterality			
Unilateral	81	42.7	0.571
Bilateral	12	33.3	
Number of PM			
Solitary	77	42.8	0.838
Multiple	16	37.5	
Maximum diameter of PM			
<30 mm	73	45.3	0.082
≥30 mm	20	29.3	
Extent of resection			
Wedge resection	77	62.7	0.925
Segmentectomy or lobectomy	16	66.7	

PM pulmonary metastasis

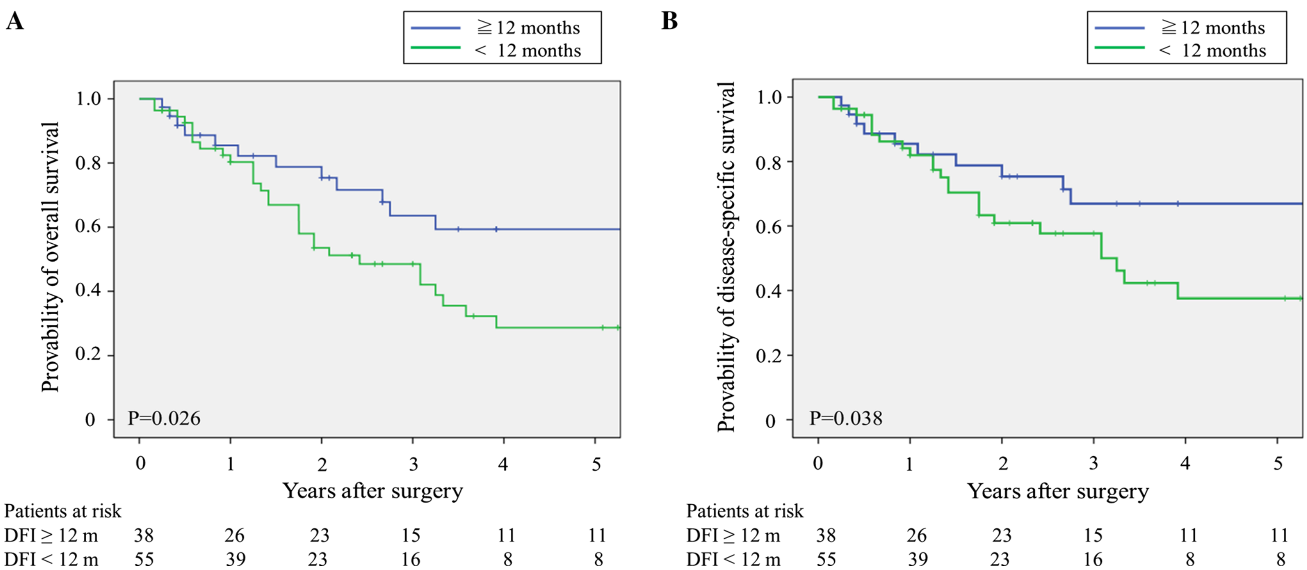

Fig. 3 **a** Kaplan–Meier overall survival curve after resection for patients with pulmonary metastasis from hepatocellular carcinoma according to disease-free interval. **b** Kaplan–Meier disease-specific survival curve after resection for patients with pulmonary metastasis from hepatocellular carcinoma according to disease-free interval

Table 3 Multivariate prognostic analysis by Cox-proportional hazard model

Variables	Favorable	Unfavorable	Hazard ratio	95 % CI	*p* value[a]
Disease-free interval	≥12 months	<12 months	2.020	1.069–3.816	0.030
Maximum diameter of PM	<30 mm	≥30 mm	1.145	0.724–1.812	0.563
Number of PM	Solitary	Multiple	1.258	0.695–2.277	0.449
History of recurrence before PM	No	Yes	1.757	0.670–3.244	0.123

[a] Cox proportional hazard model, *PM* pulmonary metastasis

>30 mm), and extent of resection (wedge resection vs anatomical resection: lobectomy or segmentectomy). Univariate prognostic analysis showed that a DFI ≥12 months is significantly associated with better OS after pulmonary metastasectomy ($p = 0.026$). And maximum diameter <30 mm also tended to be associated with favorable OS, though it did not reach statistical significance ($p = 0.082$, Table 2).

Figure 3a reveals that a DFI <12 months was associated with poorer OS after pulmonary metastasectomy (5-year OS, 28.7 vs 59.3 %, $p = 0.026$). In addition, a DFI <12 months was also associated with poorer DSS (5-year DSS, 36.2 vs. 62.5 %; $p = 0.038$; Fig. 3b).

To identify independent prognostic factors, we performed a multivariate analysis for OS using Cox-proportional hazard model. The number of PM [10, 11], DFI [12–17] and the history of recurrence before pulmonary metastasectomy [14, 15] were included in the multivariate analysis as these were reported to be associated with survival outcome of resected PM from HCC. Also, DFI and maximum diameter of PM were included because they were shown to be associated with OS in univariate analysis as above. Table 3 reveals that survival DFI ≥12 months was an independent favorable prognostic factor (HR = 2.020, 95 % CI, 1.069–3.816, $p = 0.030$). On the other hand, other factors did not reach statistical significance in multivariate analysis.

Discussion

We have shown that a DFI of 12 months or longer is an independent favorable prognostic factor in patients who underwent pulmonary resection for metastasis from HCC. It was supported by the fact that longer DFI of ≥12 months is significantly associated with better DSS as well. A possible advantage of our study is the relatively large number of cases, as this is the largest series to investigate outcomes of pulmonary resection for metastasis from HCC to date.

HCC remains a fatal cancer, despite recent progress in local therapeutic options such as molecular-targeted drugs, transcatheter arterial chemoembolization, and cytotoxic chemotherapy. Pulmonary metastases are the most common among extrahepatic metastases from HCC [18]; however, PM has not been recognized to be suitable for surgical resection. Also, survival rates of the patients with extrahepatic metastases remain poor and are refractory for systemic chemotherapy including Sorafenib [19, 20]. On the other hand, several recent literature researches suggested that pulmonary metastasectomy was an effective option in select patients [7, 8]. Thus, pulmonary metastasectomy possibly provides survival advantages to select patients, even though a possible role of pulmonary metastasectomy has not been established, and its prognostic factors have not been well documented to date. Only several small studies have reported better survival in patients who underwent pulmonary metastasectomy compared to those who underwent other treatments [21, 22]. To this end, it is meaningful to select appropriate candidates for pulmonary metastasectomy from patients with pulmonary metastases from HCC using better prognostic factors.

We conducted this study using the updated multi-institutional retrospective dataset of a Japanese cohort. Our study group previously reported that 5-year survival rate after pulmonary metastasectomy was 69.8 % [10], which was higher than the current result. Meanwhile, 5-year survival rate in the retrospective studies ranges from 27.5 to 100 % [10–17, 23, 24], suggesting survival outcome must be largely affected by patient selection and study period. It sheds light on the importance of selecting candidates for pulmonary metastasectomy. In addition, the current results showed a DFI $\geq$12 months is an independent prognostic factor, which can be useful to select candidates for prospective trials as well as clinical practice.

Several prognostic factors after pulmonary resection for PM from HCC have been reported based on variety of study design and patient population. History of recurrence [14, 15], serum alpha-fetoprotein [13, 15, 24], and the number of PM [10, 11] were commonly reported. It is reasonable because these factors might correlate to higher tumor burden. In previous reports, DFI [12–17] was shown to be a prognostic factor after pulmonary metastatectomy of HCC, which agrees with the current findings. A possible explanation for this is that DFI could reflect tumor growth speed as well as aggressiveness of metastatic tumor. Also, we should note that DFI is also associated with survival outcome following pulmonary metastasectomy from other solid malignancies [25, 26]. On the other hand, history of recurrence before pulmonary metastasectomy and the number of PM were not significant, which is consistent with one previous report [12]. In general, the majority of cases of extrahepatic recurrences have multiple organ metastases which are not provided pulmonary metastasectomy. Similarly, our cohort includes less number of cases with multiple PM. Hence, we compared DFI between the two groups according to the number of PM, revealing that cases with single pulmonary metastasis had longer DFI than those with multiple PM (Mean $\pm$ SD, 28.8 $\pm$ 8.59 vs 23.4 $\pm$ 9.80; $p = 0.009$, Supplementary Fig. 1). The number of PM could be a confounding factor in the previous study [10]. Also, it was suggested that a DFI can more strongly affect prognosis compared with the number of PM in the current series.

Progress of treatment strategy for metastatic HCC such as molecular-targeted drugs, transcatheter arterial chemoembolization, and cytotoxic chemotherapy has improved the survival outcome [11]. However, several recent studies have demonstrated that survival outcome after recurrence in patients with extrahepatic recurrence after hepatic resection remains poor, ranging from 16.2 to 24.0 % of 5-year OS after recurrence [27–29]. It is significantly poorer than those with intrahepatic recurrence [27–29]. They also mentioned that most of the patients with extrahepatic recurrence did not undergo local therapy, including surgical resection. Five-year OS after recurrence of the current cohort was better than those, although it should not be directly compared because of the differences of patient backgrounds and characteristics. It is expected that OS after recurrence will be improved as new therapeutic drugs progress in the near future. Thus, clinical significance of pulmonary metastasectomy including repeated metastasectomy must be reevaluated considering possible improvement of survival outcome. In order to clarify the efficacy of pulmonary resection for metastasis from HCC, a prospective randomized trial is necessary. To this end, our findings from relatively large cohort would be useful to select candidates for clinical trials in the future.

The present study has several limitations due to the nature of retrospective registry data including selection bias as well as numerous confounders such as long period of inclusion, disparate surgical techniques among institutions, and frequent incomplete data. Also, we could not conduct survival analysis in matched cohort because of the insufficient number of patients. Pulmonary metastasectomy from various malignancies including HCC has been widely performed based on the uncertain evidence for many years in general practice. This might be caused by lack of control data, heterogeneity of patient background, insufficient follow-up data, lack of intention to treat analysis, and so on [30, 31]. Especially in pulmonary metastasectomy for HCC, a variety of factors including former treatment, biological activity of hepatitis virus, liver function, and treatment for recurrence following pulmonary metastasectomy could affect patient outcomes. Information of these factors was hardly accessible in this study. Some retrospective studies could help develop a well-designed prospective randomized trial in the future. In spite of the above-mentioned limitations, the findings of the current study may be useful in selecting candidates for prospective trials to investigate the efficacy of pulmonary metastasectomy for HCC.

Conclusion

In conclusion, the current study showed that a DFI of 12 months or longer is an independent favorable prognostic factor in the patients who underwent pulmonary resection for metastases from HCC, with 5-year OS after recurrence of 41.4 %. Aggressive surgery for pulmonary resection from HCC could improve long-term survival outcome in highly select patients, even though this study has considerable limitations.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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