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ORIGINAL ARTICLE

Three risk factors for pulmonary metastasectomy in patients with hepatocellular carcinoma

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Abstract

Objective The outcomes of surgically treating pulmonary metastases from hepatocellular carcinoma remain unclear. Therefore, we aimed to evaluate patients with hepatocellular carcinoma who underwent pulmonary metastasectomy to assess their survival outcome and prognostic factors.

Methods This retrospective single-center study included 30 patients who underwent pulmonary metastasectomy for hepatocellular carcinoma between January 1980 and December 2016 at the National Cancer Center Hospital.

Results The 1-, 3-, and 5-year overall survival rates after pulmonary metastasectomy were 86.7%, 46.2%, and 33.6%, respectively (median survival time: 25.0 months). The univariate prognostic factors were viral hepatitis ($P=0.019$), number of pulmonary metastases ($P=0.002$), and other site recurrence before metastasectomy ($P=0.048$). Multivariate analysis using a Cox proportional hazards model revealed viral hepatitis (hazard ratio: 3.611, 95% confidence interval: 1.226–10.64; $P=0.02$) and ≥ 2 pulmonary metastases (hazard ratio: 4.031, 95% confidence interval: 1.594–10.19; $P=0.003$) to be independent prognostic factors. Subgroup analyses of the three risk factors (viral hepatitis, number of pulmonary metastases, and other site recurrence before metastasectomy) revealed that the median survival times after pulmonary metastasectomy were 66.0 and 15.5 months for patients with 0–1 risk factors and those with 2–3 risk factors, respectively ($P<0.001$).

Conclusions For patients who underwent pulmonary metastasectomy for hepatocellular carcinoma, median survival time was 25.0 months and decreased with three risk factors which included viral hepatitis, multiple number of pulmonary metastases, and the presence of other site recurrence before metastasectomy.

Keywords Pulmonary metastasectomy · Hepatocellular carcinoma · Survival outcome · Prognostic factors

Introduction

Primary hepatic cancer is an aggressive tumor with a poor prognosis and is the second leading cause of cancer-related deaths worldwide, with > 740,000 individuals affected each year. This cancer is most prevalent in southeastern Asia and parts of Africa, and the prevalence is expected to increase in the future, with hepatocellular carcinoma (HCC) being the most common primary liver tumor in Japan. Surgery, transarterial chemoembolization, percutaneous ethanol injection, radiofrequency ablation (RFA), and chemotherapy have considerably improved the prognosis of patients with HCC. However, there is a high incidence of recurrence after hepatic resection, with Poon et al. reporting a cumulative 5-year recurrence rate of 75–100% [1]. Although intrahepatic recurrence is the most common form, pulmonary metastases (PMs) account for > 50% of all extrahepatic metastases [2, 3]. Extrahepatic metastases are also associated with a poor prognosis based on the 1-year overall survival (OS) rate of 39.3% and median survival time (MST) of 8.1 months [4].

Most patients with PMs from HCC are not suitable for surgical resection owing to their advanced disease stage, low performance status (PS), severe liver dysfunction, and presence of multiple pulmonary nodules. However, since the 2000s, several studies have assessed the efficacy

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of pulmonary metastasectomy, with Yoo et al. reporting a 5-year OS rate of 37.0% and MST of 40.7 months among 45 patients with HCC who underwent pulmonary metastasectomy [5]. Furthermore, considerable attention has been recently paid to prognostic factors among patients with HCC who undergo pulmonary metastasectomy. For example, Chen et al. reported that a largest PM size of < 3 cm was the only predictor of favorable OS ($P = 0.0006$) [6]. Thus, the available reports have described variable outcomes of pulmonary metastasectomy and associated prognostic factors. The present study aimed to review our center's experience in this setting and clarify favorable indications for metastasectomy among patients with HCC.

Patients and methods

Patients and data

We retrospectively reviewed data of patients who underwent pulmonary metastasectomy for HCC at the National Cancer Center Hospital between January 1980 and December 2016. The observation period was terminated on March 31, 2017. Patients were censored on the date of death or most recent follow-up. Pulmonary metastasectomy was performed according to the following criteria: (1) no evidence of uncontrolled intrahepatic disease, (2) no evidence of extrathoracic metastasis, (3) possibility of complete pulmonary metastasectomy, (4) adequate general physical condition to permit pulmonary metastasectomy, and (5) sufficient expected pulmonary function after the pulmonary metastasectomy. These criteria were based on a modification of Thomford et al.'s principles [7]. The treatment for PM from HCC required multidisciplinary team involvement including hepatoma surgeons, hepatoma oncologists and thoracic surgeons.

Surgical treatment and postoperative follow-up

The surgical treatment was performed under general anesthesia with controlled ventilator support, and metastatic lesions were resected via pulmonary wedge resection, segmentectomy, or lobectomy. Wedge resection was generally performed for peripheral PM lesions, whereas anatomical resection (segmentectomy or lobectomy) was performed when the metastatic lesion was located deep in the pulmonary parenchyma. Anatomical lung resection was typically performed for intrapulmonary malignancies using a minimally invasive open surgery approach [8]. Based on the patient's size, a 6–8-cm incision was made near the auscultatory triangle at 2 cm below the scapula (posterolateral thoracotomy). Dissection of the mediastinal lymph nodes was not routinely performed unless enlarged lymph nodes were noted during the preoperative examination.

The surgical outcomes were evaluated in terms of OS after the initial pulmonary metastasectomy. Patients were followed up every 1–6 months using physical examination; chest radiography; blood testing, including serum AFP levels; liver ultrasonography; lung and abdominal computed tomography (CT); and 2-deoxy-2-[^{18}F]fluoro-D-glucose position emission tomography (FDG-PET) /CT, if indicated.

Clinicopathological variables and definitions

The patients' records were retrospectively searched to obtain data regarding age at pulmonary metastasectomy, sex, presence of viral hepatitis, serum AFP level before pulmonary metastasectomy, recurrence at any site before pulmonary metastasectomy, and first recurrence site. In addition, the following surgical data were collected: number and laterality of PMs, size of the largest PM, operative method, and number of pulmonary operations. DFI was calculated as the period between the primary hepatic surgery and appearance of recurrence at any site. The OS rates were calculated from the time of the pulmonary metastasectomy to the date of the most recent follow-up or death.

Statistical analysis

Survival was estimated using the Kaplan–Meier method, and univariate prognostic analysis was performed using the log-rank test. The Cox proportional hazards model was used for the multivariate analyses, which included significant variables from the univariate analyses. Differences were considered statistically significant at p values < 0.05, and all analyses were performed using IBM SPSS software (version 22; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Thirty patients (25 men) underwent curative pulmonary metastasectomy at our institution between January 1980 and December 2016 (Table 1). The median age at the initial pulmonary metastasectomy was 61.5 years (range 28–77 years). Sixteen patients were positive for hepatitis B virus-related antigens and 3 patients were seropositive for hepatitis C.

Among the 30 patients, 18 had solitary PM and 12 had multiple PMs. Twenty-three patients had unilateral PM(s) and seven had bilateral metastases. The median largest PM size was 30 mm (range 8–70 mm). The median DFI was 18.5 months (range 0–107 months). Recurrence before pulmonary metastasectomy was noted in 22 patients, with all cases involving intrahepatic recurrence. Wedge resection was performed for 20 patients, and anatomical lung

Table 1 Clinical characteristics of the patients

Characteristics	Number
Sex	
Male	25
Female	5
Viral hepatitis	
HBV	16
HCV	3
Absent	11
Disease-free interval (median: 18.5 months, range 0–107 months)	
< 12	13
≥ 12	17
Other site recurrence before metastasectomy	
No	22
Yes	8
Number of pulmonary operations	
1	21
≥ 2	9
Largest PM size (median: 30 mm, range: 8–70 mm)	
<20 mm	11
≥20 mm	19
Laterality of PMs	
Right	11
Left	12
Bilateral	7
Number of PMs	
1	18
≥ 2	12
Surgical procedure	
Wedge resection	20
Segmentectomy/lobectomy	10
The year of surgery	
Previous term (1980–1999)	12
Latter term (2000–2016)	18

HBV hepatitis B virus, *HCV* hepatitis C virus, *PM* pulmonary metastasis

resection (lobectomy or segmentectomy) was performed for 10 patients. No instances of in-hospital mortality were recorded.

Survival

The median follow-up after pulmonary metastasectomy was 22 months (range 1–110 months), and 21 patients died during the follow-up. At the latest follow-up, 23 patients experienced recurrence, with 19 patients having pulmonary recurrence and 9 patients undergoing repeat pulmonary metastasectomy for the newly detected nodules. MST after pulmonary metastasectomy was 25.0 months, and the 1-, 3-, and 5-year OS rates were 86.7%, 46.2%, and 33.6%, respectively (Fig. 1).

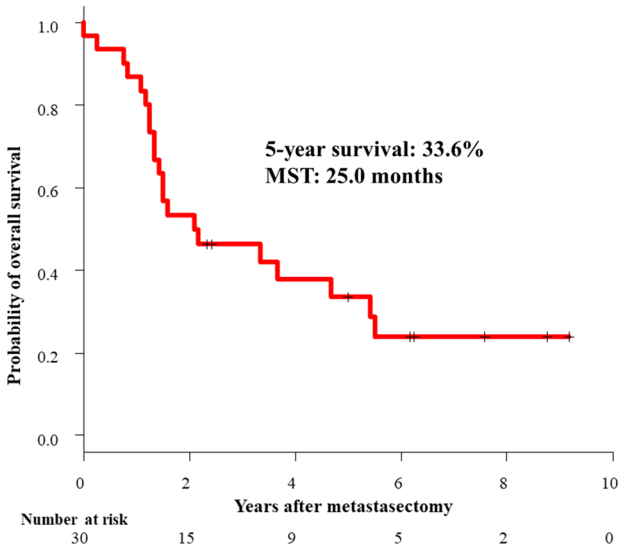

Fig. 1 Kaplan–Meier curves of overall survival after pulmonary metastasectomy for hepatocellular carcinoma. The 5-year survival rate was 33.6%, and the median survival time (MST) after pulmonary metastasectomy was 25.0 months

Univariate prognostic analysis based on Kaplan–Meier curves revealed that OS after pulmonary metastasectomy was significantly associated with viral hepatitis, number of PMs, and other site recurrence before metastasectomy. The 5-year OS was significantly higher for patients with no evidence of viral hepatitis than for those with viral hepatitis (63.6% vs. 14.2%; $P=0.019$). The 5-year OS was significantly higher for patients with a solitary PM than for those with multiple PMs (46.1% vs. 16.7%, $P=0.002$). The OS was significantly higher for patients with no recurrence before metastasectomy than for those with other site recurrence before metastasectomy (2-year OS: 59.1% vs. 37.5%, 5-year OS: 43.0% vs not reached, $P=0.048$) (Table 2). No other factors were associated with survival after pulmonary metastasectomy.

The multivariate analysis revealed that OS was independently predicted by viral hepatitis [hazard ratio (HR): 3.611, 95% confidence interval (CI): 1.226–10.64; $P=0.02$] and the number of PMs (HR: 4.031, 95% CI: 1.594–10.19; $P=0.003$). Furthermore, subgroup analyses based on three risk factors, i.e., viral hepatitis, number of PMs, and other site recurrence before metastasectomy, revealed that MSTs for patients with 0 risk factors, 1 risk factor, and 2–3 risk factors were not reached at 56.0 months, and 15.5 months, respectively ($P<0.001$) (Fig. 2; Table 3). No deaths were recorded within 1 year after the pulmonary metastasectomy among patients who had 1–2 risk factors. Two patients

Table 2 Univariate prognostic analysis using the Kaplan–Meier method

Characteristics	Number	5-year survival (%)	*p* value
Age (years)			
< 65	20	22.9	0.099
≥ 65	10	58.3	
Sex			
Male	25	31.6	0.737
Female	5	40.0	
Viral hepatitis			
Present	19	14.2	0.019
Absent	11	63.6	
AFP			
< 500 ng/mL	20	33.9	0.531
≥ 500 ng/mL	10	30.0	
Disease-free interval			
< 12 months	13	25.6	
≥ 12 months	17	38.8	0.555
Other site recurrence before metastasectomy			
No	22	43.0	
Yes	8	NR	0.048
Number of pulmonary operations			
1	21	41.7	
≥ 2	9	13.9	0.33
Largest PM size			
< 20 mm	11	47.7	
≥ 20 mm	19	25.3	0.067
Laterality of PMs			
Unilateral	23	36.1	
Bilateral	7	28.6	0.202
Number of PMs			
1	18	46.1	
≥ 2	12	16.7	0.002
Surgical procedure			
Wedge resection	20	43.3	
Segmentectomy/lobectomy	10	13.3	0.456
The year of surgery			
Previous term (1980–1999)	12	25.0	
Latter term (2000–2016)	18	37.9	0.096

AFP alpha-fetoprotein, *NR* not reached, *PM* pulmonary metastasis

with all three risk factors died because of recurrence within 13 months after pulmonary metastasectomy.

Discussion

Recent improvements in surgery, chemotherapy, and interventional therapy for HCC have resulted in improved outcomes, although recurrence after surgery for HCC remains

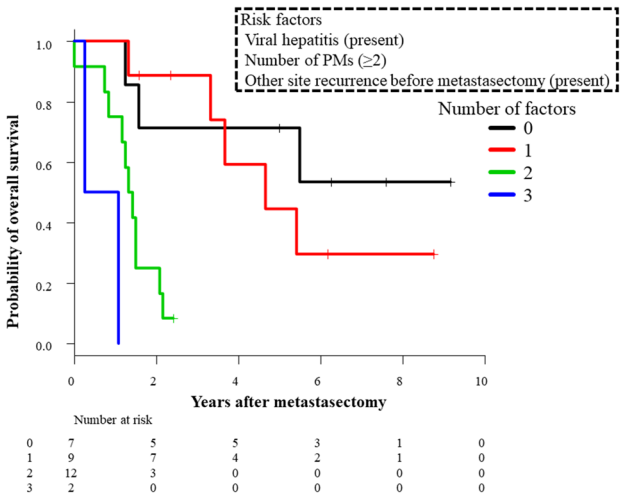

Fig. 2 Kaplan–Meier curves of overall survival after pulmonary metastasectomy for hepatocellular carcinoma according to subgroup analyses combining the three risk factors (viral hepatitis, number of PMs, and other site recurrence before metastasectomy). *PM* pulmonary metastasis

Table 3 Subgroup analyses combining the three risk factors: viral hepatitis, number of PMs, other site recurrence before metastasectomy

Factors	Number	MST	1-year survival (%)	3-year survival (%)	5-year survival (%)
0	7	NR	100	71.4	71.4
1	9	56.0	100	88.9	44.4
2	12	16.5	75.0	0	0
3	2	8.0	50.0	0	0

MST median survival time after pulmonary metastasectomy, *NR* not reached, *PM* pulmonary metastasis

common, with distant metastasis most frequently found in the lungs. There is no clear consensus regarding the optimal treatment modality for PMs in these patients, given the lack of robust evidence. Furthermore, treatment of extrahepatic metastases from HCC is complicated by the patients' low PS, severe liver dysfunction, and multiple metastases. Thus, only patients who are generally in good physical condition and have normal liver and lung functions are typically referred to the general thoracic surgery department to determine whether resection is appropriate. Nevertheless, several recent studies have assessed the efficacy of pulmonary metastasectomy and revealed 5-year OS rates that are generally in the range of 25–40% [5–10]. Our study findings are consistent with those results, suggesting that pulmonary metastasectomy is an acceptable intervention for PM from HCC.

Other treatments for PM from HCC include RFA and molecular-targeted therapies. Li et al. [11] reported 29 unresectable cases with 58 PMs from HCC that were treated using 51 RFA sessions and revealed that 1-, 3-, and 5-year OS rates after the initial RFA session were 71.6%, 27.9%, and 9.3%, respectively. In that study, MST was 26.3 months (range 3–66 months). Sorafenib therapy is the current standard of care for advanced unresectable HCCs because this multikinase inhibitor has proven efficacy against HCC that highlights the potential of molecular-targeted therapies in this setting. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol trial was the first prospective, randomized, placebo-controlled trial to confirm a survival benefit among patients with HCC based on MST values of 10.7 months in the sorafenib group and 7.9 months in the placebo group (HR: 0.68, 95% CI: 0.55–0.87; $P < 0.001$) [12].

Among patients with good general condition, normal liver and lung functions, and potentially resectable disease, the pulmonary metastasectomy was reported to improve survival [6, 10]. In contrast, RFA and sorafenib therapy are typically used for patients with low PS and/or severe liver and lung dysfunction because surgery is inadvisable for these patients. Nevertheless, the favorable results in the surgery group undoubtedly reflect a selection bias in terms of tumor burden and biology. Thus, to minimize the influence of a selection bias, Tomimaru et al. compared resection and non-resection groups of patients with similar clinicopathological factors, which revealed 3-year OS rates of 33.3% in the resection group and 0% in the non-resection group [13]. Furthermore, pulmonary metastasectomy has an acceptable safety profile because the 2014 annual report from The Japanese Association for Thoracic Surgery indicated that the 30-day postoperative mortality rate was only 0.2% [14]. Moreover, the present study did not detect any cases with major complications and there was no 30- and 90-day mortality. Thus, pulmonary metastasectomy may be acceptable for patients with good PS.

To the best of our knowledge, there are limited data regarding factors that predict prognosis after pulmonary metastasectomy for HCC. Takahashi et al. reported that a DFI of ≥ 12 months was significantly associated with favorable rates of 5-year OS (59.3% vs. 28.7%; $P = 0.026$) and 5-year disease-specific survival (62.5% vs. 36.2%; $P = 0.038$) after pulmonary metastasectomy [10]. Kawamura et al. also reported that having ≤ 3 PMs was the only factor to independently predict a good prognosis ($P = 0.048$) [15], whereas Nakagawa et al. reported that a disease-free interval (DFI) of > 1 year and serum alfa-fetoprotein (AFP) levels of < 500 ng/mL were associated with good outcomes after pulmonary metastasectomy for HCC ($P = 0.015$) [16]. In addition, Ohba et al. reported that patients with AFP levels ≥ 500 ng/mL had significantly worse rates of OS and cancer-specific survival than patients with AFP levels < 500 ng/mL ($P < 0.05$) [17]. Thus, although several small studies have evaluated pulmonary metastasectomy for HCC, they revealed different recommended indications and prognostic factors. Although the present study evaluated a relatively small number of patients, our results confirmed that OS was significantly related to viral hepatitis, number of PMs, and other site recurrence before pulmonary metastasectomy. Based on our results, the 5-year OS rates were 63.6% for patients without viral hepatitis and 14.2% for patients with viral hepatitis ($P = 0.019$), and we are unaware of any other reports that have described this relationship. Nevertheless, Nishikawa et al. implicated various non-hepatitis-related factors (e.g., nonalcoholic fatty liver disease as the hepatic manifestation of metabolic syndrome) in the development of HCC (i.e., non-B non-C HCC) and reported that patients with non-B non-C HCC who underwent curative therapy exhibited clinical outcomes comparable or superior to those of patients with hepatitis-related HCC [18].

Several studies have demonstrated that DFI is a prognostic factor. However, the present study revealed no significant difference in 5-year OS between 13 patients with DFI < 12 months and 17 patients with DFI ≥ 12 months (25.6% vs. 38.8%; $P = 0.555$).

The present study also included subgroup analyses based on the patients' number of poor prognostic factors (presence of hepatitis, number of PMs, and other site recurrence before metastasectomy), and we believe that no other clinical studies have used this scoring system to assess prognostic factors among patients who underwent pulmonary metastasectomy for HCC. The 5-year OS rate among the 16 patients with 0–1 risk factors was 59.1%, and their MST was 66.0 months, which was significantly better than the rate among the 14 patients with 2–3 risk factors (MST: 15.5 months, $P < 0.001$). Interestingly, 13 of those 14 patients experienced recurrence after pulmonary metastasectomy. These findings suggest that pulmonary metastasectomy should be avoided for patients with 2–3 of those risk factors, although it might be appropriate for patients with 0–1 risk factors based on their relatively good outcomes. In addition, pulmonary metastasectomy was safe and had a low rate of complications, which might facilitate more effective subsequent treatments.

The present study had several limitations. First, the small sample size ($n = 30$) and retrospective single-center design are associated with risks of bias, and the results should be carefully interpreted. Nevertheless, other recent studies regarding prognostic factors associated with pulmonary metastasectomy for HCC have also been limited by their small study populations. A second limitation is that most patients were selected for surgery based on their PS plus lung and liver functions. Further studies are required to elucidate other prognostic factors that may aid in the surgical

indication and prediction of oncological outcomes. A third limitation is that the time period spans several decades. As such, understanding control of disease has improved significantly with the routine use of CT and FDG-PET-CT. In addition, the treatment modalities for viral hepatitis and the use of chemotherapy target agents have changed significantly. To solve this problem, we performed analysis of the year of surgery. There were no significant differences between the previous term and the latter term (Table 2). However, the results should be carefully interpreted, with further work remains to be done in this field.

Conclusion

For patients who underwent pulmonary metastasectomy for HCC, MST was 25.0 months and decreased with three risk factors; viral hepatitis, number of PMs, and other site recurrence before metastasectomy. Nevertheless, further large-scale studies are needed to determine the effects of pulmonary metastasectomy on patients' prognosis and related prognostic factors.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

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