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## Efficacy of Surgical Resection for Pulmonary Metastases from Hepatocellular Carcinoma

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**Background:** The lung is one of the most common sites for extrahepatic metastasis from hepatocellular carcinoma (HCC). This study aimed to assess the efficacy of surgical resection for pulmonary metastases from HCC.





**Material/Methods:** The medical records of 9 patients who underwent pulmonary metastasectomy from HCC at 2 institutions were retrospectively studied, together with a review of studies reporting the outcomes of at least 5 patients in the Chinese and English languages.

**Results:** There were no perioperative deaths or major complications. The 1-, 3-, and 5-year overall survival rate after surgery was 100%, 44.4%, and 33.3%, respectively. A total of 19 studies involving 443 patients who underwent pulmonary metastasectomy for metastasis of HCC were included in the literature review. The median mortality rate was 0% (range, 0–7.1%). The median survival ranged from 10.7 to 77 (median=33.2) months, and the 5-year overall survival rate ranged from 11.5% to 75% (median=36%).

**Conclusions:** Surgical resection is a safe and effective treatment in selected patients with pulmonary metastases from HCC.

**MeSH Keywords:** **Carcinoma, Hepatocellular • Metastasectomy • Recurrence**

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## Background

Hepatocellular carcinoma (HCC) is one of the most frequent cancers worldwide and is now the third major cause of cancer-related death. Thanks to recent progress in treatment modalities, including surgical resection, liver transplantation, and locoregional therapies, the prognosis of HCC has been substantially improved [1]. However, post-treatment recurrence of HCC remains the leading cause of death in these patients. Pulmonary metastasis is the most common site of extrahepatic spread [2], and most pulmonary metastases are multiple and often considered unsuitable for surgical resection. Pulmonary metastasectomy has gradually become accepted as a surgical strategy to achieve long-term survival in selected patients, but it was reported only in a few sporadic case reports or a small series of cases with conflicting outcomes [3–10]. The aim of the present study was to assess the efficacy of surgical resection for pulmonary metastases from HCC based on a literature review and retrospective results from our patients.

## Material and Methods

### Patients

Included in this study were 9 patients who underwent surgical resection for pulmonary metastases from HCC after hepatic resection at the First affiliated Hospital of Xiamen University (Xiamen, China) and the Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University (Shanghai, China) between January 1998 and December 2012. The selection criteria for pulmonary resection were as follows: (1) without uncontrolled intrahepatic disease; (2) no other extrathoracic metastasis; (3) solitary lung metastasis; and (4) sufficient pulmonary function. The medical data of each patient were reviewed retrospectively, including age, sex, presence or absence of viral hepatitis, presence or absence of liver cirrhosis, primary tumor factors, and pulmonary metastatic factors. The disease-free interval (DFI) was defined as the time between last curative treatment for intrahepatic disease and the appearance of pulmonary metastasis. The overall survival (OS) rate from pulmonary metastasectomy was analyzed. This retrospective study was approved by the ethics committees of the 2 hospitals.

### Statistical analysis

Survival was estimated by the Kaplan-Meier method using SPSS for Windows (version 11.0; SPSS Institute, Chicago, IL, USA).

### Literature search

Electronic literature searches were performed to identify all relevant studies. Medline, PubMed, and Chinese Biological Medicine

database were searched from the time of inception to March 2014. The following MeSH search headings were used: “hepatocellular carcinoma,” “pulmonary metastasis,” and “pulmonary metastasectomy.” Only articles on humans and in the Chinese and English languages reporting the outcomes of at least 5 patients were included for assessment. Reference lists of all retrieved articles were manually searched for additional studies. Letters, reviews, abstracts, editorials, expert opinions, animal studies, and papers with fewer than 5 patients were excluded.

Data were extracted by 2 authors (Y.M.Z. and B.L.) independently using predefined criteria, including the first author, year of publication, study period, sample size, study population characteristics, and surgical outcomes. Data are presented as median (range) unless otherwise stated. Discrepancies between the 2 reviewers were resolved by discussion and consensus.

## Results

### The authors' experience

The patient group comprised 8 men and 1 woman with a median age of 58 (range 28–72) years at the time of the pulmonary metastasectomy, of whom 7 patients were positive for HBsAg; none were positive for the hepatitis C antibody; 5 patients had liver cirrhosis; 8 patients were Child-Pugh A status and 1 was B status. All primary HCC tumors were resected curatively via hemihepatectomy in 4 patients, segmentectomy in 3 patients, and partial resection in 2 patients. The median tumor diameter was 4.6 (range 3–11) cm. Microscopic invasion was observed in 6 patients.

The median DFI was 23 (range 5–53) months. Pulmonary wedge resection was performed in 7 patients and lobectomy in 2. The median diameter of the largest pulmonary metastasis was 18 (range 10–33) mm. There were no perioperative deaths or major complications. The median hospital stay was 13 (range 9–21) days.

During the follow-up period, pulmonary recurrence developed in 3 patients and intrahepatic recurrence in 4 patients. One patient underwent re-resection for pulmonary recurrence. At the end of the observation period, 6 of the 9 patients had died from secondary to recurrence (n=5) and liver failure (n=1). The median survival after pulmonary resection was 37 months, and the 1-, 3-, and 5-year OS rates were 100%, 44.4%, and 33.3%, respectively.

### Summary of literatures reporting pulmonary metastasectomy for HCC

A total of 19 publications met the inclusion criteria and were included for analysis. The demographic characteristics of the patients

**Table 1.** Characteristics of the included studies.

First author (year)	Level of evidence	Country	Period of inclusions	No. of patients (M/F)	Age (years)	HBV n (%)	HCV n (%)	LC n (%)	THL Hx/Lt/Lx	DFI (months)	BPM n (%)	SM n (%)	MTS (mm)
Lam (1998) [4]	Class II	Hong Kong	1972–1995	9 (7/2)	48.7	5/6 (83.3)	–	3/6 (50)	9/0/0	21	0 (0)	9 (100)	–
Chen (2004) [5]	Class III	Taiwan	1995–2004	6 (4/2)	41.0	6 (100)	–	3 (50)	6/0/0	27.8	2 (33.4)	1 (16.7)	–
Nakagawa (2006) [6]	Class III	Japan	1990–2005	25 (23/2)	57.2	14 (56)	5/23 (21.7)	–	25/0/0	16.3	8 (32)	11 (44)	–
Tomimaru (2006) [7]	Class II	Japan	1990–2004	8 (8/0)	66.0	3 (37.5)	3 (37.5)	–	8/0/0	32	3 (37.5)	4 (50)	21.0
Koide (2007) [8]	Class III	Japan	1980–2001	14 (13/1)	56.3	7 (50)	3 (21.4)	3 (21.4)	14/0/0	15.3	4 (28.5)	8 (57.1)	29.7
Kuo (2007) [9]	Class III	Taiwan	1990–2004	34 (30/4)	56.0	25 (73.5)	5 (14.7)	16 (47)	34/0/0	15.7	9 (26.4)	–	29.0
Bates (2008) [10]	Class III	USA	2000–2006	5 (4/1)	56.8	–	–	–	0/5/0	16.7	0 (0)	5 (100)	–
Chen (2008) [11]	Class III	Japan	1993–2005	12 (9/3)	59.0	6 (50)	3 (25)	–	10/2/0	12	0 (0)	9 (75)	20.0
Kawamura (2008) [12]	Class III	Japan	1990–2006	61 (46/15)	60.0	–	–	–	61/0/0	28.7	13 (21.3)	32 (52.4)	23.0
Kwon (2008) [13]	Class III	Korea	1999–2006	16 (14/2)	45.0	12 (75)	–	7 (43.7)	5/7/5	14	–	9 (56.2)	13.0
Liang (2008) [14]	Class III	China	1994–2005	12 (10/2)	41.0	12 (100)	0 (0)	10 (83.3)	12/0/0	28	3 (25)	7 (58.3)	32.0
Cho (2010) [15]	Class III	Korea	1999–2007	17 (14/3)	–	11 (64.7)	4 (23.5)	–	17/0/0	21.2	7 (41.1)	–	24.5
Han (2010) [16]	Class III	Korea	1998–2008	41 (29/12)	51.0	–	–	–	28/12/1	11	6 (14.6)	19 (46.3)	20.0
Lee (2010) [17]	Class III	Korea	2000–2008	32 (23/9)	50.5	27 (84.4)	3 (9.4)	13 (40.6)	21/1/10	–	9 (28.1)	–	–
Yoon (2010) [18]	Class III	Korea	1998–2008	45 (38/9)	50.9	38 (84.4)	2 (4.4)	20 (44.4)	45/0/0	5.8	1 (2.2)	34 (75.5)	15.0
Hwang (2012) [19]	Class II	Korea	1997–2009	23 (20/3)	51.3	23 (100)	–	23 (100)	0/23/0	–	4 (17.4)	13 (56.5)	2–25*
Kitano (2012) [20]	Class III	Japan	1990–2010	45 (33/12)	57.0	21 (46.6)	17 (37.7)	18 (40)	39/3/3	7.6	11 (24.4)	26 (57.7)	17
Ohba (2012) [21]	Class III	Japan	1990–2007	20 (16/4)	56.3	7/19 (36.8)	12/19 (63.1)	–	12/3/5	15	–	11 (55)	–
Zhu (2013) [22]	Class III	China	2006–2010	18 (13/5)	–	13 (72.2)	–	7 (38.8)	18/0/0	–	0 (0)	18 (100)	–

\* range. M – male; F – female; HBV – hepatitis B virus; HCV – hepatitis C virus; LC – liver cirrhosis; THL – treatment for hepatic lesion; Hx – hepatectomy; Lx – liver transplantation; Lx – locoregional therapy; DFI – disease-free interval; BPM – bilateral pulmonary metastases; SM – solitary metastases; MTS – maximum tumor size

in these studies are summarized in Table 1 [4–22]. None of these reviewed studies were randomized trials. Sixteen publications were observational studies (class III), and 3 were non-randomized comparative studies using non-surgical treatment (class II).

These papers described 443 patients who underwent pulmonary metastasectomy for HCC. Most patients were men (70.9%). The median or mean age in 17 papers providing data ranged from 41 to 66 (median=56.1) years. Assays for HBsAg

**Table 2.** Outcomes following surgical resection for pulmonary metastases from hepatocellular carcinoma.

First author	Extent of PS We/Lm or Se/We+Lm	RPS n (%)	Mortality n (%)	Median OS (months)	1-year OS (%)	3-year OS (%)	5-year OS (%)
Lam	5/3/1	2 (22.2)	0 (0.0)	42.0	100.0	–	67.0
Chen	6/0/0	2 (33.3)	0 (0.0)	37.5	83.3	66.7	66.7
Nakagawa	22/2/1	6 (24.0)	1 (3.1)	51.8	80.0	61.0	36.0
Tomimaru	4/3/1	0 (0.0)	0 (0.0)	26.5	83.3	33.3	33.3
Koide	9/4/1	6 (42.8)	1 (7.1)	19.0	71.4	26.8	26.8
Kuo	23/11/0	5 (14.7)	0 (0.0)	56.0	–	–	27.5
Bates	1/3/1	1 (20.0)	0 (0.0)	38.0	100.0	75.0	75.0
Chen	9/3/0	3 (25.0)	0 (0.0)	–	80.8	28.9	28.9
Kawamura	47/14/0	12 (19.6)	0 (0.0)	–	69.8	46.9	32.2
Kwon	–	9 (56.2)	0 (0.0)	20.0	56.0	37.0	26.0
Liang	3/5/4	1 (8.3)	0 (0.0)	24.0	83.3	46.7	21.0
Cho	15/2/0	–	0 (0.0)	28.9	64.7	29.4	11.1
Han	30/4/7	4 (7.8)	0 (0.0)	77.0	81.0	73.3	66.9
Lee	20/12/0	2 (6.2)	0 (0.0)	10.7	–	–	–
Yoon	37/8/0	–	0 (0.0)	40.7	86.0	56.3	37.0
Hwang	–	9 (39.1)	0 (0.0)	–	77.4	30.6	–
Kitano	37/80	13 (28.8)	0 (0.0)	26.5	84.0	48.0	40.9
Ohba	15/5/0	6 (30.0)	1 (5.0)	–	–	–	46.9
Zhu	18/0/0	3 (16.6)	0 (0.0)	–	100.0	–	61.1

PS – pulmonary resection; We – wedge excision, Lm – lobectomy; Se – segmentectomy; RPS – repeated pulmonary resection; OS – overall survival.

were positive in 218 (65.6%) of 332 patients with a range of 36.8% to 100% (16 papers), and for hepatitis C viral antibodies were positive in 57 (21.8%) of 261 patients with a range of 0% to 63.7% (11 papers). One hundred and twenty-three (49%) of 251 patients had liver cirrhosis (range 21.4–100%; 10 papers). In most patients, the primary lesion of the HCC was controlled by hepatectomy (n=364, 82.1%), followed by liver transplantation (n=56, 12.6%) and locoregional therapy (n=24, 5.4%).

The median or mean DFI in 16 papers providing data ranged from 5.8 to 32 (median=16) months. Lateral distribution of pulmonary metastases was reported in 17 studies involving 407 patients. Unilateral lesions were reported in 327 (80.3%) patients and bilateral lesions in 71 (19.7%) patients. The number of metastases was mentioned in 16 studies involving 360 patients. A single pulmonary metastatic lesion was reported in 216 (60%) patients, and multiple lesions were reported in

144 (40%) patients. The median or mean largest tumor size ranged from 13 to 32 (median=21) mm (15 papers).

The outcomes following surgical resection for pulmonary metastases from HCC are depicted in Table 2. The extent of pulmonary metastasectomy was reported in 17 studies involving 404 patients. The most commonly reported procedure was wedge resection (74.5%), followed by segmentectomy or lobectomy (21.6%), and wedge excision plus lobectomy (3.9%). Eighty-four (23.3%) of 359 patients underwent a repeat pulmonary resection. A total of 3 deaths were reported in all 19 studies, giving a mean mortality rate of 0.6%. The reported mortality rate in these studies ranged from 0% to 7.1% (median=0).

After pulmonary resection, the median survival ranged from 10.7 to 77 (median=33.2) months in 13 studies providing this information, and the 5-year OS ranged from 11.5% to 75% (median=36%) in 17 studies providing this information.

## Discussion

The incidence of extrahepatic metastases from HCC ranged from 13.5% to 42%. The most frequent site of distant spread is the lungs, accounting for 18–55% of extrahepatic metastases [23]. It is generally believed that any extrahepatic metastasis of HCC is contraindicated for further surgical treatment because of the poor outcome [5].

Our clinical practice in this series showed that the 5-year OS rate after pulmonary resection was 33.3% without immediate postoperative death, and our literature review of the 443 patients from the 19 studies demonstrated a low perioperative mortality rate (mean 0.6%; range 0–7.1%) with 5-year OS of 11.5–75% (median 36%). Such long-term survival cannot be achieved by non-surgical treatment [4,19]. These data suggest that surgical resection is a safe and effective treatment in selected patients with pulmonary metastases from HCC.

Minimally or less invasive resection with the maximum preservation of the lung tissue is preferred by most surgeons. As shown in the current review, wedge resection was the most commonly reported procedure (74.5%), on the basis of the rationale that the extent of pulmonary resection did not seem to affect OS [9,11,12,18,20].

Despite the good survival outcome, further recurrence remains a major oncological challenge. Repeated resections may help prolong survival of such patients. The repeated pulmonary resection rate in our cohort and in the literature is 11.1% and 23.3%, respectively.

The identification of prognostic factors associated with survival will help facilitate selection of surgical candidates who may benefit from surgery and thus improve future treatment outcomes. Unfortunately, most studies, including our series, did not address this important issue, mainly because the sample size is too small to allow a valid interpretation. Only a few studies reported diverse factors contributing to poor prognosis after pulmonary metastasectomy for HCC, including DFI (<12 or <24 months) [6,9,15], serum alpha-fetoprotein (AFP) level (>500 ng/ml before surgery or >100 ng/ml after surgery) [6,15,21], serum des-gamma-carboxy prothrombin (DCP) level (>40 mAU/ml before surgery) [20], multiple metastases ( $\geq 3$  or  $\geq 2$ ) [8,9,11,12,16,17], the maximum size of metastasis (>3 cm) [11], first recurrence [18], presence of extrahepatic/extrapulmonary metastasis [16], and HCC controlled by local treatment [17]. The significant heterogeneity among these reports may account for the inconsistency of the prognostic factors identified by the authors, including differences in the number of patients, indications for pulmonary metastasectomy, treatment

modalities for primary hepatic lesions, surgical technique, and additional therapies.

The impact of adjuvant therapy on survival after pulmonary metastasectomy for HCC remains unclear. Chen et al. [5] did not administer adjuvant chemotherapy treatment in their series of 6 patients, in whom the 5-year OS after pulmonary resection was 66.7% and 3 patients are still alive and free of the disease. Lam et al. [5] reported 9 patients who received adjuvant chemotherapy, in whom the 5-year OS was 67%, including 5 patients who were still alive, and there was no evidence of recurrence in 4 of them. They therefore suggested that systemic chemotherapy be given to all patients after pulmonary metastasectomy in order to inhibit occult metastasis. However, their updated study [24] reported that there was no significant difference in survival after excision of extrahepatic recurrence between patients who received adjuvant systemic chemotherapy and those who did not. In our study, no adjuvant chemotherapy was given after either primary hepatectomy or lung resection for metastasis. Currently, it seems unlikely to perform a randomized controlled trial in any center to clarify the survival benefit of adjuvant therapy because of the small number of patients. In addition, most cytotoxic anticancer agents are too toxic for patients with HCC, particularly those with underlying chronic liver dysfunction.

The indications for surgery in pulmonary metastasis from HCC seem different from those in other lung metastases. Generally speaking, surgery for pulmonary metastasis is not indicated in cases in which the recurrent focus is recognized at the primary site. Compared with previous studies, the criteria for tumor resectability in our study were more strictly defined by excluding patients with  $\geq 2$  lung metastases. It is possible that tumor multiplicity is a marker of additional undetected micrometastatic disease in the lung. The International Registry of Pulmonary Metastasis reported in 1990 that single metastasis is an important prognostic factor based on the result obtained from 5206 cases of pulmonary metastasectomy of various primary tumors [25].

## Conclusions

According to our experience and other recent studies in the literature, surgical resection is a safe and effective treatment in selected patients with pulmonary metastasis from HCC.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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