



## Original Research

# Therapeutic significance and indications of pulmonary metastasectomy for hepatocellular carcinoma following liver resection



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## ABSTRACT

**Background:** To explore the therapeutic significance and indications of pulmonary metastasectomy (PMT) in hepatocellular carcinoma (HCC) patients with pulmonary metastasis (PM) following liver resection (LR).

**Patients and methods:** PM-HCC patients who underwent LR were retrospectively enrolled, and survival outcomes and prognostic factors were analyzed. Patients were divided into PMT and non-PMT group, and propensity score matching (PSM) analysis was used for survival comparison. Prognostic analysis and survival comparisons were performed specifically in PMT patients.

**Results:** Ninety-seven patients were enrolled, among which twenty-six underwent PMT while seventy-one did not. Survival outcome was superior in PMT group compared to non-PMT group (33.5 vs. 10.5 months) ( $p = 0.003$ ), while no statistical difference was found after PSM analysis (33.5 vs. 11.2 months) ( $p = 0.138$ ). Synchronous PM-HCC, serum alpha fetal protein  $\geq 400$  ng/ml at PM diagnosis, no intrahepatic treatments (LR, ablation or transarterial chemoembolization) after LR, intrahepatic recurrence or metastasis at repeated PM diagnosis were inferior independent prognostic factors in PMT patients ( $p < 0.05$ ). Superior survival outcomes were seen in candidate PMT patients when corresponding indications were satisfied ( $p = 0.014$ ,  $p = 0.005$ ).

**Conclusion:** PMT might provide potential survival benefits in well selected PM-HCC patients who underwent LR. Well designed, multi-institutional studies with larger patient number were still to be required.

## 1. Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide, being one of the major causes of cancer related death, due to the high incidence of recurrence or metastasis, coupled with the unsatisfied progress in exploring effective strategies for early diagnosis and treatments [1]. Pulmonary metastasis (PM) is the most common type of extrahepatic metastasis in HCC, accounting for 30%–50% of the metastatic cases [2–4]. However, prognosis of PM-HCC patients remains poor with a median survival ranged from six to ten months [4,5].

Well controlled primary intrahepatic tumors and adequate interventions for metastatic intrapulmonary tumors were considered crucial

for superior prognosis in PM-HCC patients [4,5]. Comprehensive treatments have been applied and exhibit favorable effects controlling primary intrahepatic tumors [6]. Liver resection (LR), a therapeutic modality with curative intents, is considered of a priority in HCC patients with resectable lesions [6], and was reported to provide superior survival outcome in PM-HCC patients [7]. Therefore, management of PM became a realistic problem frequently confronted with in PM-HCC patients whose primary intrahepatic tumors were controlled by LR. Sorafenib is generally recommended as an effective drug for PM-HCC patients, while the response rate is limited [8–10]. Pulmonary metastasectomy (PMT), an aggressive therapeutic modality, was adopted as an alternative therapeutic option for PM lesions [11–13], while no

**Abbreviations:** PM, pulmonary metastasis; HCC, hepatocellular carcinoma; PMT, pulmonary metastasectomy; LR, liver resection; PSM, propensity score matching; OS, overall survival; AFP, alpha fetal protein; IHRM, intrahepatic recurrence or metastasis; DM, distant metastasis; ECOG, Eastern Cooperative Oncology Group; TNM, Tumor Node Metastasis; BCLC, Barcelona Clinic Liver Cancer; IHT, intrahepatic treatments; TACE, transarterial chemoembolization; ST, systemic therapies; SC, supportive care; IQR, interquartile range; CI, confidential interval

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**Table 1**  
Baseline characteristics and survival statistics of PM-HCC patients who underwent LR.

Characteristics	Overall (n = 97)	PMT(n = 26)	non-PMT(n = 71)
<b>Host characteristics</b>			
Gender (Male/Female)	78/19	21/5	57/14
Age (years)*	48.2 (39.2–55.5)	49.0 (36.1–53.5)	47.6 (39.2–56.1)
Hepatitis B virus infection <sup>#</sup>	85/12	21/5	64/7
Liver cirrhosis <sup>#</sup>	60/37	17/9	43/28
ECOG score (0/1/2)	90/7/0	24/2/0	66/5/0
Child-Pugh score (5/6/7/8)	78/11/5/3	21/4/1/0	57/7/4/3
<b>HCC characteristics</b>			
Serum AFP (< 25/≥ 25 ng/ml)	79/18	20/6	59/12
Maximum HCC diameter (cm)*	10.0 (7.0–12.0)	8.3 (6.0–12.5)	10.0 (7.0–12.0)
HCC number (Single/Multiple)	63/34	22/4	41/30
Hepatic vein invasion (Negative/Vv1/Vv2/Vv3)	34/45/17/1	10/11/4/1	24/34/13/0
Portal vein invasion (Negative/Vp1/Vp2/Vp3/Vp4)	25/38/3/22/9	9/10/0/4/3	16/28/3/18/6
Regional lymph node metastasis <sup>#</sup>	16/81	3/23	13/58
DM <sup>#</sup>	15/82	3/23	12/59
T factor (T1/2/3/4)	17/15/46/19	7/4/8/7	10/11/38/12
TNM staging (I/II/III/IV)	14/12/41/30	7/4/10/5	7/8/31/25
BCLC staging (A/B/C)	26/11/60	11/2/13	15/9/47
Histological grading (G1/2/3)	20/32/45	8/6/12	12/26/33
<b>PM characteristics</b>			
ECOG score (0/1/2)	39/55/3	25/1/0	14/54/3
Child-Pugh score (5/6/7/8/9/10)	67/19/4/2/1/4	21/4/1/0/0	46/15/3/2/1/4
Serum AFP (< 25/≥ 25 ng/ml)	69/28	14/12	55/16
PM distribution (Segment/Lobe/Unilateral/Bilateral)	9/11/15/62	5/8/8/5	4/3/7/57
Maximum PM diameter (cm)*	1.2 (0.8–2.0)	1.5 (1.0–2.8)	1.1 (0.8–1.7)
PM number (1/2/3/More)	16/9/8/64	13/5/5/3	3/4/3/61
Hilar or mediastinal lymph node metastasis <sup>#</sup>	19/78	4/22	15/56
Synchronous PM-HCC <sup>#</sup>	12/85	3/23	9/62
IHRM <sup>#</sup>	69/28	9/17	60/11
DM(Extra-hepatic and -pulmonary) <sup>#</sup>	17/80	0/26	17/54
<b>Perioperative treatments and outcomes</b>			
HCC-PM interval(m)*	6.3 (2.4–17.9)	17.6 (9.1–27.3)	5.0 (2.1–13.5)
Post-LR IHRM <sup>#</sup>	83/14	17/9	66/5
Post-LR IHT (LR/Ablation/TACE/ST or SC)	12/37/73/20	5/13/13/5	7/24/60/15
Post-PM IHT (LR/Ablation/TACE/ST or SC)	11/16/38/46	5/7/9/12	6/9/29/34
Overall DM(Extra-hepatic and -pulmonary) <sup>#</sup>	32/65	7/19	25/46
PMT modality (Wedge/Lobe/Pneumonectomy)	–	23/2/1	–
Repeated PM <sup>#</sup>	–	19/7	–
IHRM at repeated PM diagnosis <sup>#</sup>	–	13/13	–
Repeated PMT <sup>#</sup>	–	3/23	–
<b>Survival statistics</b>			
Post-PMT follow-up period(m)*	–	11.8 (4.2–32.1)	–
Overall follow-up period of PM(m)*	8.5 (3.9–19.6)	14.8 (5.9–38.7)	7.5 (3.2–14.5)
Outcome (Dead/Alive/Withdraw)	60/14/23	12/8/6	48/6/17
Post-PMT OS(m)**	–	28.2 (12.7–43.7)	–
Post-PMT OS rates (%) <sup>##</sup>	–	73.5/43.1/32.3	–
OS of PM(m)**	13.2 (9.2–17.2)	33.5 (0.0–76.2)	10.5 (8.3–12.7)
OS rates of PM(%) <sup>##</sup>	52.6/22.6/9.6	77.3/48.3/29.0	43.5/13.9/5.5

\*Median(IQR); IQR, interquartile range; \*\*Median(95%CI); CI, confidential interval; <sup>#</sup>Positive/Negative; <sup>##</sup>1/3/5year; m, months; PM, pulmonary metastasis; HCC, hepatocellular carcinoma; LR, liver resection; PMT, pulmonary metastasectomy; ECOG, Eastern Cooperative Oncology Group; AFP, alpha fetal protein; DM, distant metastasis; TNM, Tumor Node Metastasis; BCLC, Barcelona Clinic Liver Cancer; IHRM, intrahepatic recurrence or metastasis; IHT, intrahepatic treatments; TACE, transarterial chemoembolization; ST, systemic therapies (systemic chemotherapy or sorafenib); SC, supportive care; OS, overall survival.

definite guidance was available in the current clinical guidelines [8–10]. A series of retrospective studies showed that it might provide potential survival benefits in well selected patients, while most of which were non-controlled studies, and definite therapeutic indications had not been elaborated [14–16].

In this study, detailed clinical features, survival outcomes and prognostic factors of PM-HCC patients who underwent LR were analyzed. Besides, case control study was achieved using propensity score matching (PSM) analysis to evaluate the therapeutic significance of PMT. Additionally, prognostic analysis was performed to investigate potential independent prognostic factors specifically in patients who underwent PMT. Furthermore, survival comparisons were performed between candidates and non-candidates for PMT according to different criteria from previous studies and current study, which might provide evidence for the establishment of surgical indications for PMT.

## 2. Patients and methods

### 2.1. Patients

PM-HCC patients who underwent LR were retrospectively enrolled at our Institute during January 2000 and December 2015. Patient exclusion criteria were as follows: (1) With other malignancies or lethal comorbidities; (2) Medical intervention related death; (3) Underwent intrapulmonary treatments other than PMT; (4) With incomplete clinical information. The following clinical data were collected: (1) Host characteristics; (2) HCC characteristics; (3) PM characteristics; (4) Perioperative treatments and outcomes (Table 1). Data collections were accomplished by two independent investigators in our group, and an additional third independent investigator was invited to achieve a consensus if discordance existed. This study was reviewed and

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