

Result of surgical treatment for pulmonary metastasis from hepatocellular carcinoma

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SUMMARY

Objective:

Evaluating result of surgical treatment, prognosis factors to survival time in pulmonary metastasis (PM) from Hepatocellular carcinoma (HCC) patients at Cho Ray hospital.

Method: A retrospective review of surgical treatment of PM from HCC patients at Cho Ray hospital from 11/2015 – 5/2020.

Results: Total 24 PM from HCC patients were surgical treatment. The mean tumor size is 2.7 ± 1.1 cm (range 1- 6 cm). The mean FDI (free disease interval) is 23.37 ± 21.23 (2 – 108) month. Most of patients were thoracoscopic wedge resection of pulmonary metastasis. There was no mortality and major complication, 2 patients with seroma. Follow up, 7 patients died. The mean survival time 25.7 ± 4.7 tháng (1- 46 tháng). The rate of 1 year, 2 years, 3 years overall survival is 86.5 %, 46.2% and 30.8 respectively.

Conclusion:

Surgical resection is a safe and effective treatment in selected patients with pulmonary metastases from HCC. The patients with previous resection of HCC have survival time longer than those with transdermal ablation. The patients with serumAFP level > 100 ng after HCC resection need to be screening chest CT Scans for PM

Key word: pulmonary metastasis (PM), hepatocellular carcinoma (HCC)

INTRODUCTION

Pulmonary metastasis is lung tumor metastasized from other extra-thoracic primary cancer such as HCC, colon cancer... Recently, there are many advanced changes in treatment of pulmonary metastasis. The treatment is not only curative treatment but the goal of treatment also changes from living without disease to living with systemic disease.

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and the third leading cause of cancer-related death. Pulmonary metastasis is the most frequent site of distant metastasis from HCC. Most of pulmonary metastases are multiple lesions and unsuitable for resection. Pulmonary metastasis from HCC accounts for 10% HCC patient who were curative surgery [6]. Resection of PE have been accepted as a surgical procedure in selected HCC patients. Cautious indication will improve the survival quality and prolong long – term survival of the patients with PE from HCC [1,9]. However, many reports have been presented only in limited cases with diverging results. Thus, the goal of our study was to evaluate the efficacy of resection for PE from HCC and clinical prognosis factors in patients with PE from HCC.

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Material and method

A retrospective method of all patients who had been resected PM from HCC in Thoracic surgical department at Cho Ray hospital from 11/2015 – 5/2020 was study.

The patients with the post operative pathologic result of benign lung disease or primary lung cancer were excluded from study.

Pulmonary metastasis from HCC were identified on X ray or a chest computed tomography (CT) Scans during follow up the primary HCC patients. The primary HCC patients were treated by hepatic resection, percutaneous or transcatheter local therapy.

Preoperative preparation, pulmonary function test and blood test were routinely performed for all patients.

The selection criteria for pulmonary resection were as follows: (1) control of HCC; (2) no other distant extrathoracic metastasis; (3) solitary lung metastasis that are thought to be completely resectable; and (4) an adequate cardio-pulmonary reserve.

Surgical procedure

Patients' medical status including the liver function values or potential risk factors for general anesthesia and operation were tested. Single lung ventilation anesthesia was performed. The PM was resected either by VATS or open surgery. VATS lung wedge resection is preferred procedure in order to reserve pulmonary function and minimize the surgical risk to the patients with chronic liver diseases. Lobectomy was indicated when large tumor or central tumor that was unable to do wedge resection. All PM were done frozen section biopsy. Pleural drainage before

closing the chest. All complication and mortality were evaluated.

The clinical outcomes were evaluated post-operatively in first month, at regular 3-month, 6 month-intervals with laboratory tests and radiological imaging studies, such as a X ray, conventional lung CT scans until ending study (8/2020) or death patients. Survival, recurrent, mortality and morbidity were checked.

The medical data of each patient were reviewed retrospectively, including age, sex, history of viral hepatitis, presence or absence of liver cirrhosis, primary tumor factors and pulmonary metastatic factors (characteristics of tumor on X ray, CT Scans, pathologic result). Operative time, blood loss, time of drainage, length of hospital stay, complications such as: air leak, bleeding, pneumonitis, death.

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 time after the pulmonary metastasectomy was analyzed with respect to the DFI the therapeutic modality used for the primary lesion (surgical resection, RF or MW ablation) and other clinical factors.

Statistical analysis:

The survival curves were calculated using the Kaplan-Meier method, and the survival according to the prognostic factors was compared using a log-rank test. (Using Cox's proportional hazard model, clinical prognostic indicators predicting increased survival of patients with HCC and pulmonary metastasectomy were tested). The statistical study was performed with

SAS statistical software package (version 6.12, SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant. This retrospective study was approved by the ethics committees of the hospitals.

RESULT

Total 52 patients HCC who were found a lung mass during follow up after management hepatic were PM resection. There were 24 patients diagnosed with a PM-HCC on pathologic examination, the other are benign tumor or lung cancer. There were 22 males (91.7%) vs. 2 females (8.3%), mean age 56.67 ± 12.2 years (range 31-79).

All patients presented with a mass on X ray or CT Scans, 3 patients had a chest pain (12.5%).

The past history of hepatitis: 19 patients, HBV: 13 (54.2%), HCV: 6 (25%). There was 1 patient with diabetes mellitus type II, 1 patient with hypertension. The median DFI was 23.37 ± 21.23 (range 2 – 108) months.

α -feto protein: 5 patients had a normal value, 19 patients (79.2%) with the high value (> 100)

The cardiac-pulmonary function was available for surgery. [Tif mean 80.2 ± 7.6 (63-94); FEV1 mean: 2.74 ± 0.71 (1.55 – 4.01); FVC mean: 3.44 ± 0.71 (1.68 – 4.9); EF $> 60\%$]

ECG: 2 patients (8.3%) cardiac ischemia, 2 patients (8.3%) atrial arrhythmia, 1 patients (4.2%) ventricular arrhythmia.

Chest X ray only identified lung mass in 11 patients (45.8%). All patients were taken CT Scans, 4 of them were got PET – CT but there were no distant extrathoracic metastasis. 1 pts

with a central lung mass was did bronchoscopy.

All patients were reviewed the HCC before pulmonary surgery with abdominal ultrasound, MRI.

The average PM size was 2.7 ± 1.1 cm (range 1-6).

All primary HCC tumors were treated curatively. There were 19 patients resected HCC (hemihepatectomy in 17 patients, resection of HCC tumor and RFA later 2 patients). 5 patients were transdermal ablation of HCC. RFA: 1 patients (4.2%), MW (microwave): 2 patients (8.3%), RFA and TACE: 2 patients (8.3%)

VATS Pulmonary wedge resection was performed in 22 patients (91.6%) and lobectomy in 2 patients (8.4%) with 1 VATS and 1 open. There were no perioperative deaths or major complications. The median hospital stay was 3.08 ± 0.88 (range 2–6) days. The mean operative time 1.91 ± 0.62 hour (1.5 - 4). The mean time of pleural drainage 2.08 ± 0.21 day (2-3)

During the follow-up period, all patients were good in first vist after 1 month. At the end of the observation period (8/2020), only 21 patients still were observed (no adjuvant therapy), 3 patients missing after first visit. 14 pts were survival (58.33%), 7 patients had died from secondary to extra thoracic recurrence (n=1) liver recurrence (n=4), pulmonary recurrence (n=1), cardiac failure (n=1). The median survival after pulmonary resection was 25.7 ± 4.7 (1- 46) months, and the 1-, 2-, and 3-year OS rates were 86.5 %, 46.2% và 30.8% respectively.

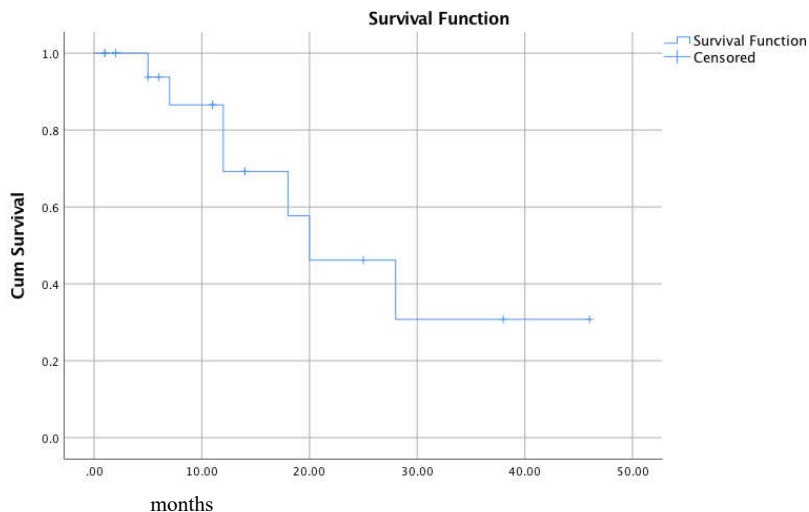


Figure1: Survival time of PM – HCC patients

Prognostic factors influence the survival time

When the prognosis after the pulmonary metastasectomy was compared according to the therapeutic modality for primary HCC, the survival was found to be significantly higher in patients who had undergone resection of hepatic tumor than in those who had received other treatments, such as a surgical resection and locoregional therapy (Figure 3). In addition, among clinical factors, FDI < 12 month (Figure 2), negative evidence of an HBV infection (Figure 4), α -feto protein >100 (Figure 5) the diameter of PM tumor (Figure 6), showed longer survival but no statistical significant (log rank test).

- FDI

FDI < 12: (6 patients) The mean survival time 29.7 ± 7.1 months and FDI ≥ 12 tháng (18 patients) the mean survival time 23.7 ± 4.7 months. (P = 0.6).

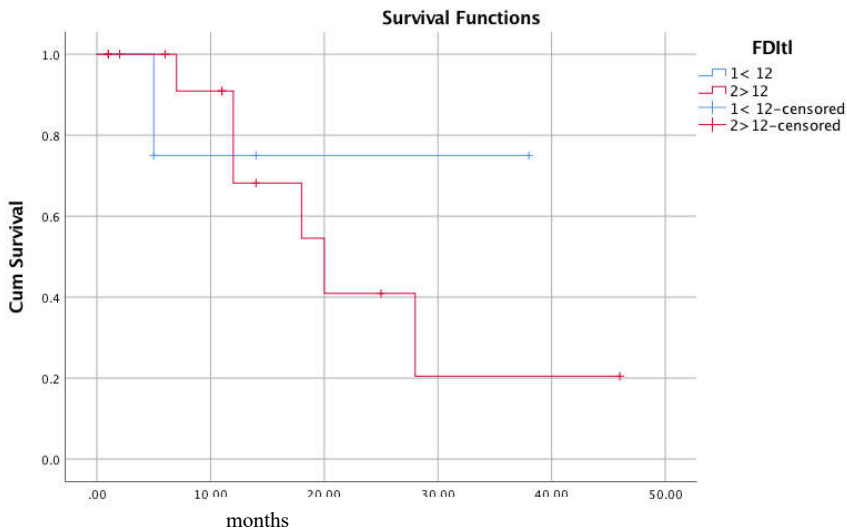


Figure 2: FDI < 12 months

- Procedure of treatment HCC

Resection of hepatic tumor (15 patients), the mean survival time: 30.06 ± 5.5 months. Resection of HCC tumor and RFA later (2 patients), the mean survival time: 9.5 ± 2.5 months. Transdermal ablation (4 patients), the mean survival time: 18.0 ± 0.0 months. ($P = 0.05$). (log rank test)

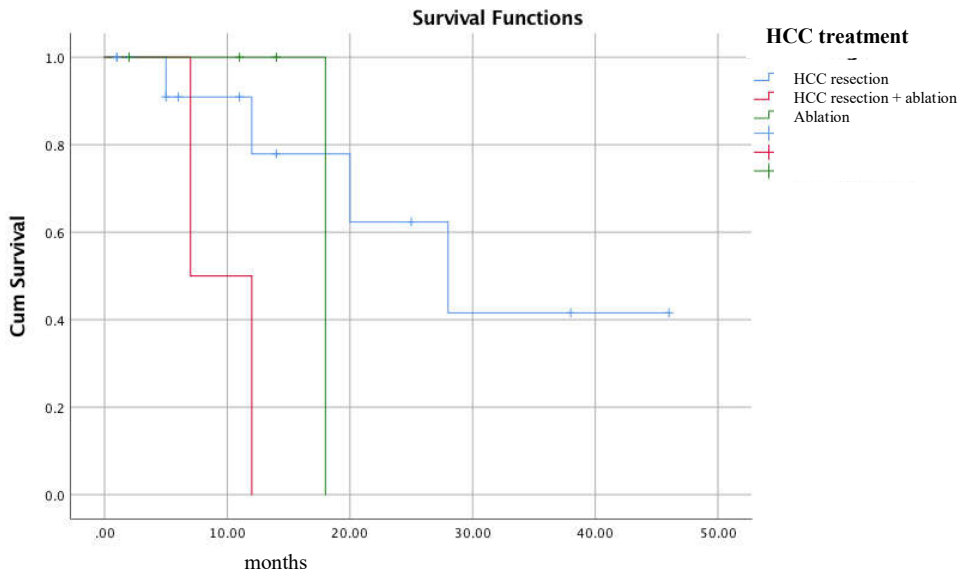


Figure 3: Procedure of treatment HCC

- AFP

AFP < 100ng (5 patients) the mean survival time 20 ± 4.3 months and AFP ≥ 100 ng (16 patients) the mean survival time 28.2 ± 4.4 months ($P = 0.7$).

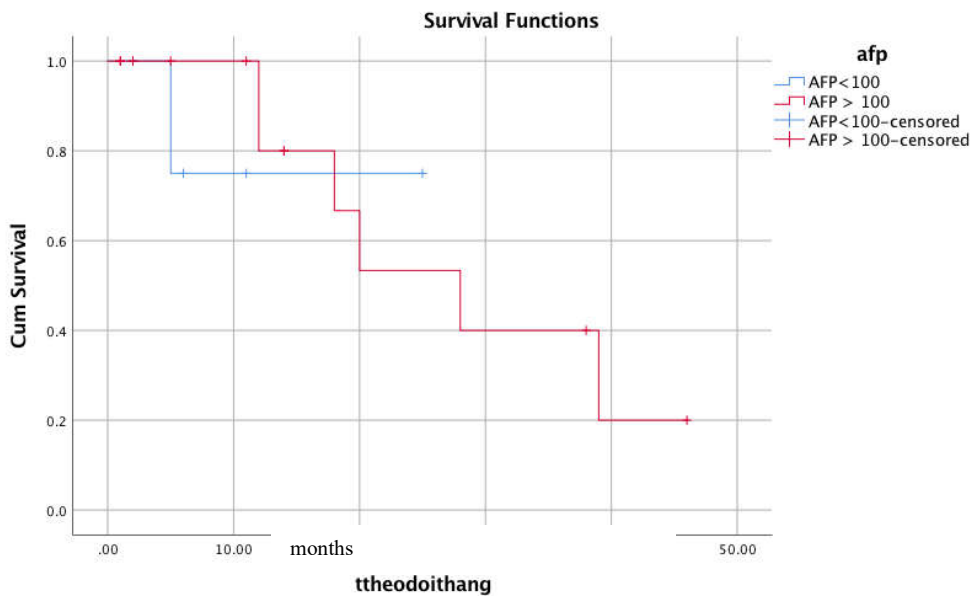


Figure 4: AFP value

- History of hepatitis

Group without history of hepatitis: (4 patients) the mean survival time 28 ± 0.0 months and group with history of hepatitis (17 patients) the mean survival time 28.2 ± 4.8 months. (P = 0.6)

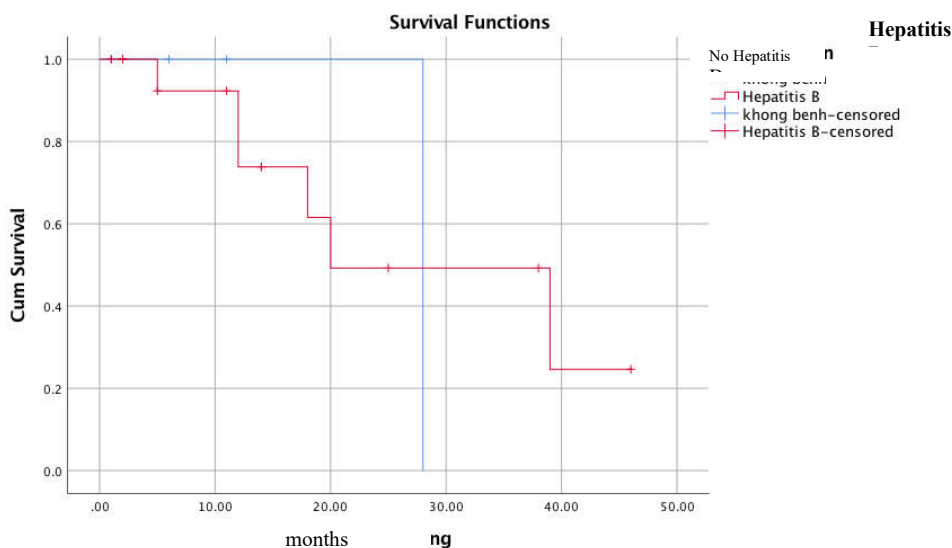


Figure 5: Comparison of survival in patients with HBV hepatitis-related HCC after pulmonary metastasectomy

- Diameter of PM tumor

Diameter of PM tumor < 2cm: (6 patients) the mean survival time 24 ± 6.3 months and Diameter of PM tumor ≥ 2 cm (15 patients) the mean survival time 28.8 ± 4.9 months. (P = 0.76)

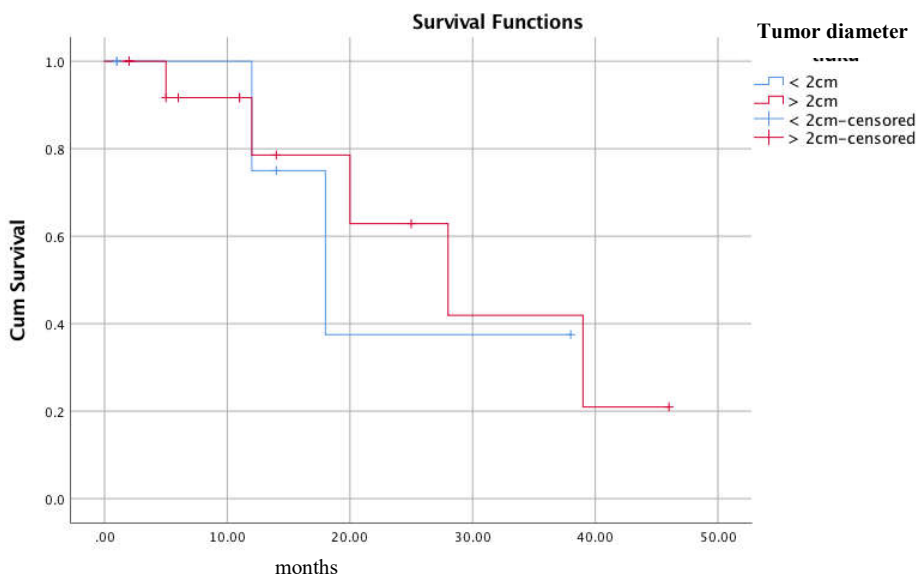


Figure 6: Diameter of PM tumor

DISCUSSION

HCC is one of the most least survival disease in cancer. This also is a common disease in Asia where had a high rate of hepatitis B. Although hepatic lesion was curative treatment, the rate of distant metastasis from HCC ranged from 13.5% - 42%. The most frequent site of distant metastasis is the lung accounting for 18–55% [9]. The distant metastasis from HCC was a worst survival prognosis though there were many progresses in treatment. It is generally believed that any distant metastasis of HCC is contraindicated for further surgical treatment because of the poor outcome [2]. Unlike a PM from other cancer, it is difficult to manage PM-HCC because it is commonly associated with advanced liver disease or the patients cannot tolerate systemic chemotherapy [4]. The studies about surgical treatment of PM was more increased and had demonstrated that surgical treatment of PM was effective in prolong survival time. The HCC patients had longer survival prognosis due to advance in diagnosis, treatment and follow up. Thus, surgical treatment of PM – HCC is a good indication for patient. [8].

Screening PM - HCC

The incidence of PM – HCC was diagnosed depended on the size of PM, imaging technique, time of follow up and the therapeutic modality of HCC. [2,7]. Because most of PM – HCC patients usually have not pulmonary symptoms until they progress to growth disease, chest CT scan is essential for making an early and accurate diagnosis of a PM-HCC.

In our study, most PM – HCC patients were diagnosed during periodic follow-up after treatment HCC. Because our hepatic surgical department

have a schedule of close follow-up examination for HCC patients. Almost patients were identified the PM while they had no lung symptoms. Only 3 patients presented chest pain (12.5%).

All HCC patients were found a PM on chest CT Scans, the rate of PM diagnosed on chest X ray was 45.8%. Although PET is effective in detecting distant metastasis in other solid tumors, the diagnostic accuracy of primary HCC showed limited clinical significance. In the study of Jong-Bum Kwon and cs, there were 5 true metastatic lesions in 3 patients were confirmed by pathological examination but PET-CT did not show any diagnostic accuracy for these lesions, which might be due to the small lesions or the low standardized uptake values (SUV) [3,5].

Another factor which suggested early detection of distant metastasis from HCC was the α -feto protein level. However, Jong-Bum Kwon reported the α -feto protein level was elevated by more than 20 ng/mL in only 8 (50%) of the 16 patients with a PM- HCC. The reason why only 50% of patients had an elevated α -feto protein level might be due to a small lesion (< 1 cm) or severe liver dysfunction [5]. We found 19 of the 24 patients (79.1%) in our series had α -feto protein level was elevated more than 100 ng/mL

The FDI in our series was 20.8 months thus we need to indicate chest X ray or CT Scans in 3 month-interval visit for HCC patients during 2 year after hepatic curative treatment, especially in patients with α -feto protein level that elevated more than 100 ng/mL.

Pulmonary metastasectomy from HCC

The survival prognosis of PM –HCC patients without surgical treatment were low. The

1 year- OS (overall survival) rate accounted for approximately 20%-30% with systemic chemotherapy. The surgical treatment of PM had increased the average survival for PM – HCC patients [5]. A pulmonary metastasectomy of an HCC increases the median survival or long-term survival. The indication of pulmonary mastasectomy of HCC is different from PM of other cancer. Lung reservative pulmonary metastasectomy is preferred procedure by most thoracic surgeon. VATS 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]. Although the outcome or prognosis of VATS was not different from open surgery, VATS made the patients more comfortable and the reoperation of pulmonary metastasectomy could perform again [5].

Our series had shown that all PM – HCC patients only had a solitary PM on imaging. 19 of the 24 patients with history of hepatitis (HBV and HCV) but the hepatic function was normal. The cardiacpulmonary function was suitable for surgery. 22 patients were VATS wegde resection. 2 cases were lobectomy because of the central tumor and pleural adhesion. The mean length of hospital stay was 3.08 ± 0.88 ngày. There were no major complication and post-operative death, 2 patients (13.3%) were wound seroma.

In series of Yan-Ming Zhou showed that the 5-year OS rate after pulmonary resection was 33.3% without immediate postoperative death. The 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 se- lected patients with pulmonary metastases from HCC [9].

The post-operative follow-up time in our study was not long but the mean survival time was 25.7 ± 4.7 , the longest survival patient was 46 months (he is alive). The 1,2,3 years survival rate was 86.5 %, 46.2% and 30.8% respectively (Figure 1). There were 7 deaths, 4 from hepatic recurrent, 2 metastasized to trachea,contralateral lung, 1 died from heart failure.

Prognostic factors associated with survival after resection of PM

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. [9]

The International Registry of Pulmonary Metastasis,in 1990, reported solitaryPM was an important prognostic factor. That report was replied on the result of resecting 5206 PMpatients. [9].Surgical resection of solitary PM patients had better survival than those with multinodules PM. Although no certain prosgnostic factors,several clinical or pathological factors contributing to poor prognosis after pulmonary metastasectomy for HCC have been reported including DFI (<12 or <24 months), serum alpha-fetoprotein (AFP) level (>500 ng/m before surgery or >100 ng/ml after surgery), serum des-gamma-carboxy prothrombin (DCP) level (>40 mAU/ml before surgery), multiple metastases, the maximum size of metastasis (>3 cm), first

recurrence, presence of extrahepatic/extrapulmonary metastasis, and HCC controlled by local treatment [9]. However, the differences in the number of patients, indications for pulmonary metastasectomy, treatment modalities for primary hepatic lesions, surgical technique, and additional therapies among the reports may be controversial in the prognostic factors identified by the authors.

In reports of Yan Ming Zhou, liver transplantation, negative evidence of an HBV infection, and well differentiation of HCC and curative resection of HCC were significant prognostic indicators but the statistics was unclear. Maybe the quantity of PM – HCC patients was too small [9].

As shown in this series, the clinical factors such as DFI (<12 months), serum alpha-fetoprotein (AFP) level (< 100 ng/ml before surgery), no history of HBV infection, the maximum size of metastasis (< 2 cm) had a longer survival but the result of statistics was not significant ($P > 0.05$). Only the resection of HCC was a significant prognosis factor in survival comparing with other procedure of HCC treatment ($P < 0.05$) (Figure 3).

Generally, patient selection according to the prognostic factors, such as single metastasis and resection of primary HCC, is essential for a survival benefit by surgery.

CONCLUSION

According to our experience and other recent studies, surgical resection is a safe and effective treatment in selected patients with pulmonary metastasis from HCC. The patients with previous resection of HCC have survival

time longer than those with transdermal ablation. The patients HCC with serum alpha-fetoprotein (AFP) level > 100 ng after HCC resection need to be screening chest CT Scans for PM.

TÀI LIỆU THAM KHẢO

1. Chen YJ, Hsu HS, Hsieh CC et al: Pulmonary metastasectomy for hepatocellular carcinoma. *Chin Med Assoc*, 2004; 67: 621–24
2. Gwak GY, Jung JO, Sung SW et al: Long-term survival after pulmonary metastasectomy of hepatocellular carcinoma; treatment outcome or natural history? *Hepatogastroenterology*, 2004; 51: 1428–33
3. Hustinx R. PET imaging in assessing gastrointestinal tumors. *Radiol Clin North Am* 2004; 42: 1123-39,
4. Jang JW, Park YM, Bae SH, Choi JY, Yoon SK, Chang UI, Nam SW, Kim BS. Therapeutic efficacy of multimodal combination therapy using transcatheter arterial infusion of epirubicin and cisplatin, systemic infusion of 5-fluorouracil, and additional percutaneous ethanol injection for unresectable hepatocellular carcinoma. *Cancer Chemother Pharmacol*, 2004; 54: 415-420
5. Jong-Bum Kwon, Khun Park, Young-Du Kim, Jong-Hee Seo, Seok-Wan Moon, Deog-Gon Cho, Yong-Wan Kim, Dong-Goo Kim, Seung-Kew Yoon, Hyeon-Woo Lim. Clinical outcome after pulmonary metastasectomy from primary hepatocellular carcinoma: Analysis of prognostic factors. *World J Gastroenterol*, 2008 October 7; 14(37): 5717-5722

6. Kanda M, Tateishi R, Yoshida H et al: Extrahepatic metastasis of hepato-cellular carcinoma: incidence and risk factors. *Liver Int*, 2008; 28: 1256–63

7. Kuo SW, Chang YL, Huang PM et al: Prognostic factors for pulmonary metastasectomy in hepatocellular carcinoma. *Ann Surg Oncol*, 2007; 14: 992–97

8. McCormack P. Surgical resection of pulmonary metastases. *Semin Surg Oncol*, 1990; 6: 297-302

9. Yan-Ming Zhou* Xiao-Feng Zhang* FengYu^[1]Xiao-Bin Liu Lu-Peng Wu BinLi, Jia-Mei Yang. Efficacy of Surgical Resection for Pulmonary Metastases from Hepatocellular Carcinoma. *Med Sci Monit*, 2014; 20: 1544-1549.