

Prolonged survival in selected patients following surgical resection for pulmonary metastasis from hepatocellular carcinoma

C.-M. LAM, C.-M. LO, W.-K. YUEN, C.-L. LIU and S.-T. FAN

Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong

Correspondence to: Professor S.-T. Fan

Background Pulmonary metastasis is the commonest site of extrahepatic spread from hepatocellular carcinoma (HCC). The aim of the present study was to evaluate the efficacy of surgical management in patients with solitary pulmonary metastases from HCC.

Methods This was a retrospective study of patients with HCC admitted for hepatectomy from July 1972 to June 1995. The records of patients who had a pulmonary resection for histologically proven pulmonary recurrence after curative hepatectomy were selected for analysis.

Results In the study interval, 380 patients with HCC underwent hepatectomy. Some 48 patients (12.6 per cent) developed pulmonary metastases documented pathologically or radiologically. Nine (seven men and two women) were suitable for curative pulmonary resection. The median disease-free survival between hepatectomy and appearance of the lung metastasis was 21 months. The median survival after pulmonary resection was 42 months, and the 1-, 2- and 5-year survival rates were 100, 78 and 67 per cent respectively.

Conclusion Pulmonary resection for metastases from HCC resulted in long-term survival in these highly selected patients.

Hepatocellular carcinoma (HCC) is common in Asia and is the second most common cancer causing death in Hong Kong¹. With the recent advances in diagnostic modalities, perioperative management and surgical technology, more patients are suitable for hepatic resection². Furthermore, the perioperative morbidity and mortality rates after hepatic resection have improved in recent years^{3,4}. The long-term outcome of patients with HCC remains poor because of a high incidence of recurrence after hepatic resection.

Although intrahepatic recurrence predominates, pulmonary metastasis is the commonest site of extrahepatic spread⁵. The role of surgery for a solitary pulmonary metastasis is not known. The aim of the present study was to evaluate the efficacy of surgery in treating patients with a solitary pulmonary metastasis after curative hepatic resection.

Patients and methods

Between July 1972 and June 1995, 380 patients with HCC underwent hepatic resection. The preoperative investigations, operative technique and postoperative management have been documented elsewhere^{3,4}. All patients were followed up regularly at intervals of 1–3 months with physical examination, chest radiography and liver biochemistry tests. Since 1984 follow-up has included regular measurement of serum α -fetoprotein concentration and percutaneous ultrasonography of the liver remnant. Computed tomography of the lung was done if the chest radiograph was abnormal.

Patients with a solitary pulmonary metastasis and no concomitant intrahepatic recurrence were selected for surgery. After resection of the pulmonary recurrence, patients received adjuvant chemotherapy (six doses of intravenous epirubicin

60 mg/m²) and careful life-long follow-up. Further pulmonary resection was performed for patients with reappearance of another solitary metastasis if there was no liver recurrence. Patients with uncontrolled liver disease or multiple pulmonary metastases were offered chemotherapy.

Both disease-free survival and overall survival were measured from the date of hepatic resection. The survival rates were calculated according to Kaplan and Meier⁶.

Results

Among the 380 patients who had hepatectomy for HCC, 48 (12.6 per cent) developed pulmonary metastases documented radiologically or pathologically. Nine patients, seven men and two women, were suitable for curative pulmonary resection because their hepatic disease was cleared or well controlled.

The clinical parameters of these nine patients are summarized in *Table 1*. The median disease-free interval between hepatectomy and appearance of the lung metastasis was 21 months. There was no operative or hospital death among the nine patients who had pulmonary resection. Two patients (6 and 9) developed hepatic recurrence before the discovery of pulmonary metastases, but the hepatic recurrence was treated successfully by transarterial oily chemoembolization (TOCE) and intralesional alcohol injection respectively. Three patients (2, 3 and 5) developed recurrent disease in the liver after the pulmonary resection. Two patients (3 and 6) each developed a second pulmonary metastasis and required repeat thoracotomy for resection at 12 and 13 months after the first lung resection.

The median duration of follow-up after hepatectomy was 53 months. The median survival after pulmonary resection was 42 months. The 1-, 2- and 5-year survival rates after hepatectomy were 100, 78 and 67 per cent respectively. Five patients were still alive and four of them had no evidence of recurrent disease. One patient (no. 9)

Presented to the 14th Asia Pacific Cancer Conference in Hong Kong, November 1997

Paper accepted 20 March 1998

Table 1 Clinical details of patients who had pulmonary resection for metastases from hepatocellular carcinoma

Patient no.	Sex	Age (years)	Hepatic lobectomy	Related liver disease	Disease-free survival (months)	Pulmonary resection	Survival (months)	Outcome
1	M	68	Right	n.a.	20	R lower lobectomy	22	Dead, free from disease
2	M	62	Left	n.a.	51	Wedge excision	93	Dead with disease in liver
3	M	25	Right extended	HBsAg ⁺	10	Wedge excision and right lower lobectomy	34	Dead with disease in liver
4	F	33	Right	n.a.	11	Wedge excision	15	Dead, free from disease
5	M	58	Right	HBsAg ⁺ , cirrhosis	11	Wedge excision	80	Alive with disease in liver
6	M	38	Right extended	HBsAg ⁺ , CAH	21	Wedge excisions	53	Alive with no evidence of disease
7	M	45	Right	HBsAg ⁺ , CAH	23	Wedge excision	81	Alive with no evidence of disease
8	M	60	Right	Cirrhosis	23	R lower lobectomy	74	Alive with no evidence of disease
9	F	50	Left extended	HBsAg ⁺ , cirrhosis	26	L lower lobectomy	127	Alive with no evidence of disease

HBsAg⁺, hepatitis B antigen positive; CAH, chronic active cirrhosis; n.a. not available

is alive more than 8 years after pulmonary resection (more than 10 years after hepatectomy) and remains disease free.

Thirty-nine patients developed pulmonary metastases but were not suitable for resection because of the presence of uncontrolled liver disease or multiple pulmonary metastases. Twenty of them accepted systemic chemotherapy. Twenty-three of the 39 patients had documented hepatic recurrence in addition to the pulmonary metastases. The median disease-free interval before the appearance of lung metastases was 8 months. The median survival after diagnosis of the pulmonary metastases was 14 months, and the 1-, 2- and 5-year survival rates after hepatectomy were 42, 32 and 10 per cent respectively.

Discussion

The postoperative morbidity and mortality rates of patients who have hepatectomy for HCC have been improving in recent years^{3,4}. After successful resection, the recurrence rate is disappointingly high; as many as 80–85 per cent of patients succumb to recurrent disease within the first 18 months of hepatectomy⁷.

Although the lung is the commonest site for extrahepatic spread from HCC, only a few case reports exist in the English literature describing the management of this condition^{8,9}. Therefore, the treatment strategy and prognosis of patients with pulmonary metastases from HCC are largely unknown.

Some investigators consider any extrahepatic recurrence of HCC to be a contraindication for further treatment¹⁰. Indeed, the result of treatment for extrahepatic recurrent HCC is poor. In a study of 34 patients with extrahepatic metastases (21 pulmonary) treated with chemotherapy, the median survival and 1-year survival rate were 4.6 months and 20 per cent respectively¹¹. The effect of chemotherapy on pulmonary metastases is difficult to predict. Some of the present patients had a good response to systemic chemotherapy and a prospective study is underway to document the result.

The authors have reported previously that surgical resection is effective in selected patients with an isolated extrahepatic recurrence of HCC and offers the only chance of long-term survival¹². Therefore, with this rationale, patients with a solitary pulmonary metastasis were managed actively.

Most pulmonary metastases of HCC are multiple¹³ and are not amenable to surgical resection. Solitary pulmonary metastases may be encountered occasionally. If considered resectable, the patient should be investigated to exclude the presence of other metastasis, especially in the liver remnant, before embarking on surgery. However, if the hepatic recurrence can be cleared by re-resection or controlled by local ablation using intralesional alcohol injection or TOCE, pulmonary resection for solitary metastasis may still be considered.

Even when a metastasis seems solitary, it is generally assumed that occult metastases are present. Therefore, systemic chemotherapy was given to all patients after resection of the pulmonary metastasis. The patients who had surgical resection for a curable pulmonary metastasis had a survival rate comparable to that of patients without recurrence after hepatectomy. However, this was a highly selected group of patients as the pulmonary metastases appeared late, a median of 21 months after hepatectomy, in contrast to 8 months in the patients with irresectable disease.

Although the number of patients suitable for resection of a pulmonary metastasis after curative hepatectomy for HCC is small, some long-term survivors will benefit. An active approach to the management of resectable pulmonary metastases from HCC is justified in selected patients.

References

- 1 Hong Kong Government. *Department of Health—Annual Report 1993–94*. Hong Kong: Hong Kong Government Printer, 1995.
- 2 Matsuda Y, Ito T, Oguchi Y, Nakajima K, Izukura T. Rationale of surgical management for recurrent hepatocellular carcinoma. *Ann Surg* 1993; 217: 28–34.

- 3 Lai ECS, Fan ST, Lo CM, Chu KM, Liu CL, Wong J. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. *Ann Surg* 1995; 221: 291–8.
- 4 Fan ST, Lai ECS, Lo CM, Ng IOL, Wong J. Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Arch Surg* 1995; 130: 198–203.
- 5 Lee YT, Geer DA. Primary liver cancer: pattern of metastasis. *J Surg Oncol* 1987; 36: 26–31.
- 6 Kaplan EL, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958; 53: 457–81.
- 7 Johnson RC. Hepatocellular carcinoma. *Hepatogastroenterology* 1997; 44: 307–12.
- 8 Hino H, Higashi T, Veki T, Nakatsukasa H, Ooguchi S, Ashida K *et al*. Disappearance of pulmonary metastases by OK-432 treatment in a case of hepatocellular carcinoma. *Acta Med Okayama* 1993; 47: 289–92.
- 9 Sasaki Y, Imaoka S, Shibata T, Wada H, Nagano H, Ishikawa *et al*. Successful surgical management of pulmonary and adrenal metastases from hepatocellular carcinoma. *Eur J Surg Oncol* 1991; 17: 84–90.
- 10 Shimada M, Takenaka K, Gion T, Fujiwara Y, Kajiyama K, Maeda T *et al*. Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. *Gastroenterology* 1996; 111: 720–6.
- 11 Okusaka T, Okada S, Ishii H, Nose H, Nagahama H, Nakasuka H *et al*. Prognosis of hepatocellular carcinoma patients with extrahepatic metastases. *Hepatogastroenterology* 1997; 44: 251–7.
- 12 Lo CM, Lai ECS, Fan ST, Choi TK, Wong J. Resection for extrahepatic recurrence of hepatocellular carcinoma. *Br J Surg* 1994; 81: 1019–21.
- 13 Tsai GL, Liu JD, Siau CP, Chen PH. Thoracic roentgenologic manifestations in primary carcinoma of the liver. *Chest* 1984; 86: 430–4.