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Case Report

Synchronous primary lung cancer and hepatic cancer versus hepatic metastasis: a report of three cases and literature review

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Abstract: To date, reports regarding synchronous double malignancies of primary lung cancer and hepatic carcinoma is limited, which could be misdiagnosed empirically as lung cancer with distant metastasis. However, a timely diagnosis and staging of synchronous multiple malignancies is essential for the optimal choice of therapy. An elderly patient was admitted in our hospital because his CT showed both pulmonary and liver lesions, who was initially misdiagnosed as lung cancer with hepatic metastasis after bronchoscopic biopsy. But the liver mass was enlarged after the first cycle of chemotherapy, and then the liver biopsy revealed his correct diagnosis as synchronous primary lung cancer and hepatocellular carcinoma. Therefore, biopsy of the lesions in different organs should be performed separately to avoid misdiagnosis. Herein, three cases are presented and discussed.

Keywords: Synchronous multiple primary cancers, multiple primary malignancies (MPM), hepatocellular carcinoma (HCC)

Introduction

In the era of precision medicine, personalized oncology spreads fast with limits and uncertainties. Multiple primary malignancies (MPM) may be presented independently as synchronous (within 6 months) or metachronous (at least 6 months later) [1]. The prevalence of MPM is reported to be 0.73~11.7%, while nearly 30~40% of them are synchronous tumors [1-4]. Lung cancer is one of the most prevalent synchronous tumors [3]. Besides, a population-based analysis indicates that, liver metastasis is common from small cell lung cancer, whilst bone metastasis is common from pulmonary adenocarcinoma. And liver metastases confer the worst prognosis [5]. However, patients with concurrent advanced primary lung cancer and isolated liver nodule are easy to be empirically misdiagnosed, consequently, the treatment of second primary neoplasm probably be delayed. Three representative cases with synchronous pulmonary and hepatic malignancies in our hospital are presented, with the aim to diminish empirical misdiagnosis during differential diagnosis of these patients.

Cases presentation

Case 1

A 66-year-old male patient was admitted for irritating cough for six months, followed by fatigue, inappetence and loss of weight for one month. He had no history of alcohol or tobacco consumption. He had been working as a coal miner for more than ten years. His physical examination indicated nothing abnormal except rough breathing. To rule out pulmonary infection, laboratory tests for white blood cell counts, hepatic and renal function were performed, which were all in normal range. His serum tumor markers were as follows: cytokeratin 19 fragment (CYFRA21-1; normal range, <3.3 ng/mL), 22.89 ng/mL; alpha fetoprotein (AFP; normal range, ≤25 ng/mL), 1.69 ng/mL; squamous cell carcinoma (SCC; normal range,

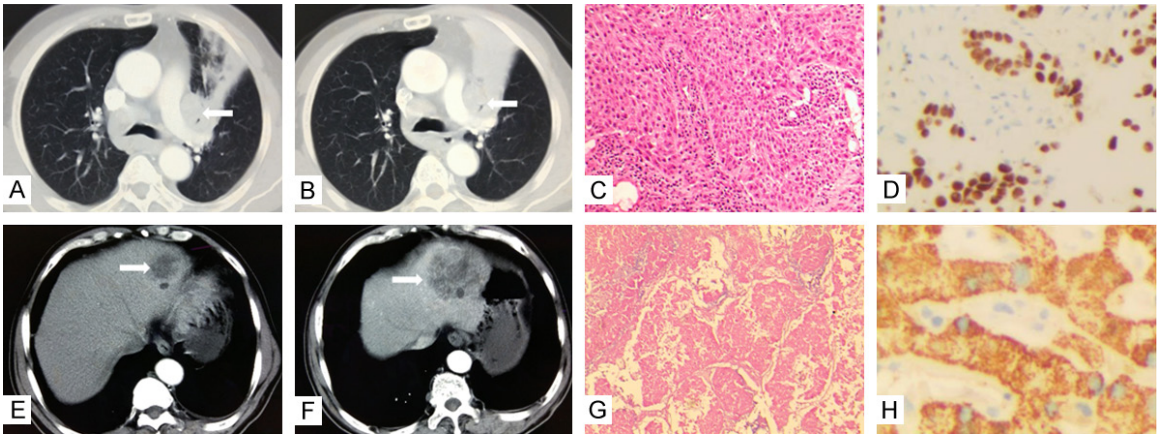

Figure 1. Case 1 was diagnosed as concurrent primary lung cancer and liver cancer. The CT scan on admission revealed central type pulmonary cancer (A), Stable disease of the lung cancer after initial chemotherapy (B); Biopsy confirmed primary squamous carcinoma of lung by pathological test (H&E staining; magnification, ×100) (C) and positive immunohistochemical staining of P63 (D) (magnification, ×200); The CT scan showed concurrent liver lesion in left hepatic lobe (E); Enlarged hepatic lesion was shown after initial chemotherapy (F); Second biopsy of the liver indicated synchronous primary HCC by pathological test (G) (H&E staining, ×100) and positive immunohistochemical staining of hep parl (H) (magnification, ×400).

<1.5 ng/mL), 1.44 ng/mL; carcinoembryonic antigen (CEA; normal range, <3.4 ng/mL), 23.35 ng/mL; and neuron specific enolase (NSE; normal range, <16.3 ng/mL), 17.62 ng/mL. His Child-Pugh grade of hepatic function was A. Computed tomography (CT) of the chest on admission showed central type pulmonary mass, with atelectasis and encasement of the left pulmonary artery (**Figure 1A**). While his abdomen CT indicated a large lesion located in the left lobe of the liver measuring 48 mm in size (**Figure 1E**). Further bone emission computed tomography (ECT) and cranial magnetic resonance imaging (MRI) excluded metastases to the bone, brain, or adrenal gland. Bronchoscopic biopsy confirmed the diagnosis of squamous carcinoma after pathological and immunohistochemical staining (**Figure 1C**), which was positive for cytokeratin (CK)18, Ki67 (20%) and P63 as shown in **Figure 1D**, and negative for CK7, thyroid transcription factor 1 (TTF-1), neural cell adhesion molecule (CD56), epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Based on these findings, the patient was empirically misdiagnosed as pulmonary squamous carcinoma with hepatic metastasis, subsequently, two cycles chemotherapy of gemcitabine (1250 mg/m^2 of body surface area, day 1 and day 8) and cisplatin (75 mg/m^2 of body surface area) was administrated.

However, re-evaluation of the lesions by CT revealed that the lung lesion was stable (**Figure 1B**), but the hepatic lesion was enlarged (**Figure 1F**). CT-guided percutaneous liver biopsy revealed typical histologic features of hepatocellular carcinoma (HCC) after pathological and immunohistochemical staining (**Figure 1G**), which indicated positive expression of CD34, Ki67 (5%) and hep parl as shown in **Figure 1H**, followed by negative expression of CEA, AFP, S-100, synaptophysin (Syn) and CD-56. Therefore, his diagnosis was corrected as concurrent primary pulmonary squamous carcinoma and HCC. Then his therapeutic regimen was changed to be 3 cycles of chemotherapy using paclitaxel liposome (135 mg/m^2 of body surface area), cisplatin (75 mg/m^2 of body surface area), leucovorin (200 mg per day, days 1~4) and tegafur (800 mg per day, days 1~4). Subsequently, Apatinib, an oral tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor-2 (VEGFR-2), was administrated for 3 months (425 mg per day). This patient has survived for 11 months up to now without systemic dissemination in CT images after chemotherapy.

Case 2

A 76-year-old male patient was presented for 1-month of hemoptysis. He was a 20 pack-years smoker. Abnormal serum tumor markers

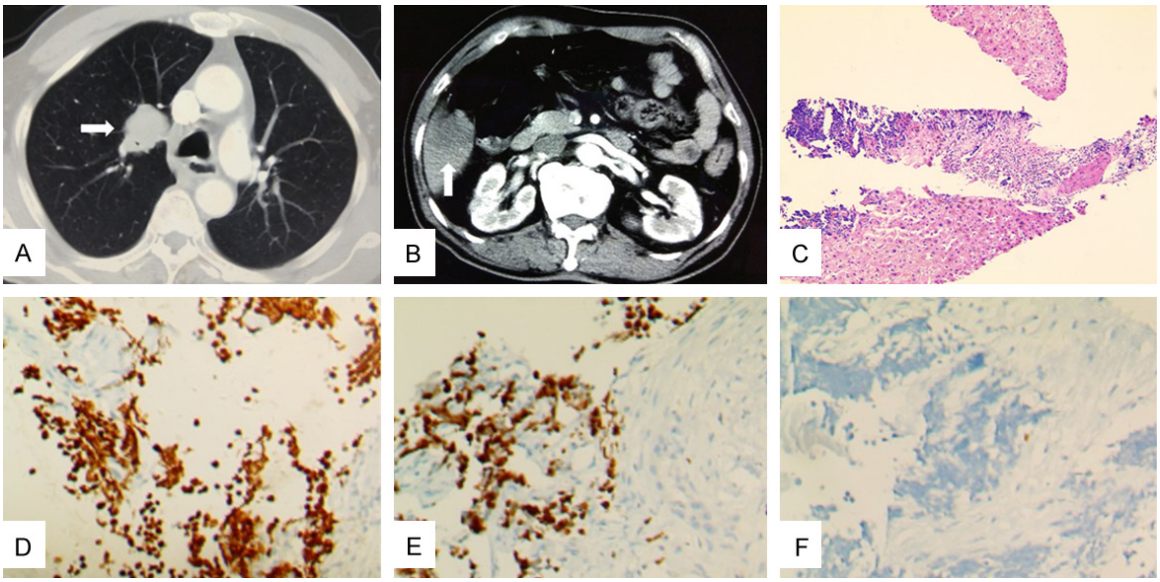

Figure 2. Case 2 was diagnosed as hepatic metastasis from primary lung cancer. The CT scan revealed central type pulmonary tumor (A), and liver lesion in the right hepatic lobe (B); CT-guided liver biopsy revealed hepatic metastasis from primary small cell lung cancer by pathological test (C) (H&E staining; magnification, ×100); Immunohistochemical test showed positive expression of chromogranin A (D) and Syn (E), but negative hep parl (F) (magnification, ×200).

were as follows: NSE, 19.23 ng/mL; SCC, 2.52 ng/mL; pro-gastrin-releasing peptide (ProGRP), 360.8 gp/ml. Enhanced CT scan indicated central type pulmonary tumor (**Figure 2A**), and an isolated large liver lesion located in the right hepatic lobe (**Figure 2B**). Biopsy under bronchoscopy failed to obtain enough specimen for pathological diagnosis. Then CT-guided percutaneous liver biopsy was performed, which led to the correct diagnosis of primary small cell lung cancer (SCLC) with liver metastasis after pathological staining of the liver specimen (**Figure 2C**). Further immunohistochemical staining demonstrated positive expression of Ki67 (60%), TTF-1, Syn and chromogranin A as shown in **Figure 2D** and **2E**, and negative expression of CK5/6, P40, Napsin A, AFP and hep parl as shown in **Figure 2F**. Therefore, the patient was diagnosed as extensive stage of SCLC. Subsequently, two cycles of chemotherapy using etoposide (100 mg per day, days 1~4) and cisplatin (75 mg/m^2 of body surface area) were administrated. However, his CT scan showed a partial response (PR) of the primary pulmonary lesion, but progressive disease (PD) of the hepatic metastasis, in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST). Based on these findings, the hepatic lesion was suspicious of a mixture of synchronous primary SCLC and primary liver cancer. A second liver biopsy and immunohistochemical staining could be helpful to confirm the origin of the hepatic lesion, but the patient refused further treatment and lost to follow up.

Case 3

A 63-year-old male patient was admitted for fatigue and low back pain for 1 month. The CT scan on admission revealed an isolated pulmonary nodule of 10 mm in size in the left upper lobe with typical spicule sign (**Figure 3A**), and a concurrent larger liver mass measuring 27 mm in diameter in the left hepatic lobe (**Figure 3B**). Serum tumor markers of CYFRA21-1, AFP, SCC, CEA, CA125 and NSE were in normal range, but the positron emission tomography (PET) scan revealed bony metastasis. Besides, CT-guided percutaneous fine-needle biopsy of the liver revealed adenosquamous carcinoma of pulmonary origin after histopathological staining (**Figure 3C**). Further immunohistochemical staining demonstrated positive expression of CK 7, CK5/6, P63, Ki67 (5-10)% and TTF-1 as shown in **Figure 3D** and **3E**, followed by negative CD56, anaplastic lymphoma kinase (ALK) and hep parl as shown in **Figure 3F**, which confirmed his correct diagnosis as hepatic metastasis originated from pulmonary adenosquamous carcinoma (sarcomatoid carcinoma). Su-

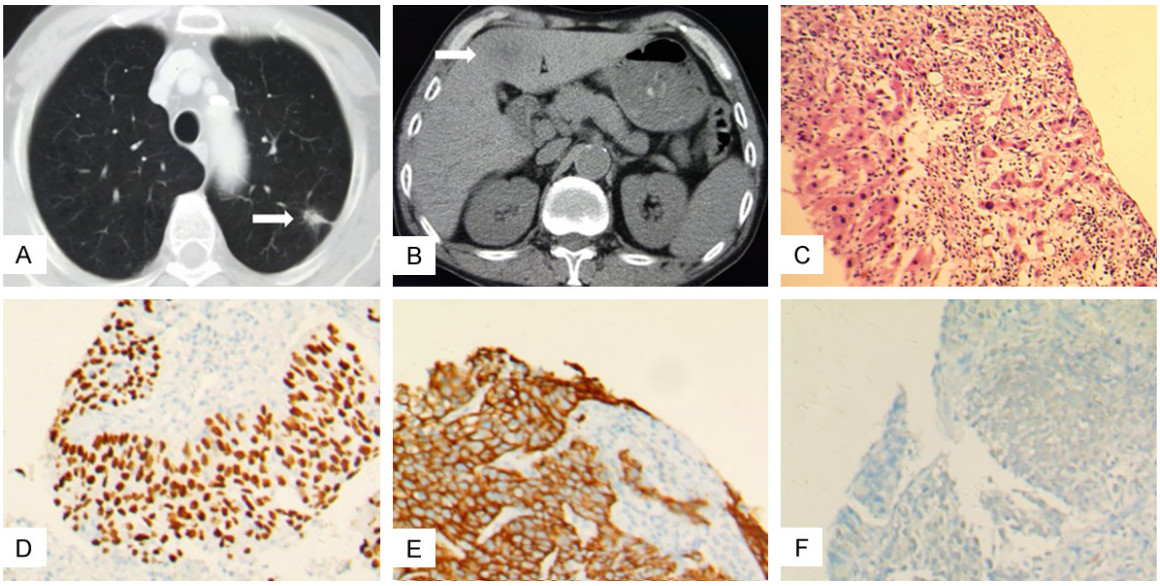

Figure 3. Case 3 was diagnosed as hepatic metastasis from primary lung cancer. The CT scan revealed an isolated small pulmonary nodule in the left upper lobe (A), and a concurrent liver mass in the left hepatic lobe (B); CT-guided liver biopsy revealed hepatic metastasis from lung adenosquamous carcinoma by pathological test (C) (H&E staining; magnification, ×100); Immunohistochemical test indicated positive TTF-1 (D) and CK5/6 (E), but negative hep parl (F) (magnification, ×200).

bsequently, systemic chemotherapy using 4 cycles of pemetrexed (500 mg/m^2 of body surface area) plus cisplatin (75 mg/m^2 of body surface area), followed by 4 cycles of concurrent gemcitabine (1000 mg/m^2 of body surface area, day 1 and day 8), cisplatin (75 mg/m^2 of body surface area) and bevacizumab (Avastin, Roche Pharma (Schweiz) Ltd., 10 mg/Kg of body weight) was administrated. This patient has survived for 16 months after his diagnosis up to now.

Discussion

Differentiation between second primary cancer and metastasis from the first cancer is often difficult but clinically important, because the therapy and prognosis are distinct. Accordingly, there are several issues need to be elucidated to diminish empirical misdiagnosis of patients with synchronous malignancies, in accordance with the basic principles of precision medicine.

Firstly, a combined approach involving clinical, molecular (genetic) and immunohistochemical analysis of the specimens may be effective for the differential diagnosis between primary and metastatic cancer. MRI shows higher sensitivity than CT, which should be preferred for the diagnosis of HCC [6]. In addition, the features of lung cancer on CT images include notching, air bronchogram, pleural indentation and spiculation. PET is useful for detection of extrahepatic metastases or recurrence of HCC [7]. Hepatic mass without any history of hepatitis virus infection should be carefully investigated before giving a diagnosis of liver cancer.

Secondly, a high or increasing serum alpha-fetoprotein (AFP), Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) and des-gamma-carboxy prothrombin (DCP) can be predictive of the development of HCC [8], and the other tumor markers for liver cancer include Golgi Protein 73 (GP73) and fucose-studded GP73 [9]. However, the sensitivity and specificity of AFP have some shortcomings. Cell-free circulating tumor DNA has been widely investigated as a noninvasive surrogate of tissue biopsy for tumor-related genomic alterations [10]. Detection of recirculating tumor cells in peripheral blood as “liquid biopsy” might be valuable tumor markers [11]. Furthermore, comprehensive genomic profiling technologies have the power to distinguish synchronous primary non-small cell lung cancer (NSCLC) from intrapulmonary metastasis [12]. Meanwhile, correct differential diagnosis of hepatic metastasis and primary HCC is sometimes difficult, and CT-guided biopsy is safe and decisive.

Thirdly, liver metastases appear in 20-30% of NSCLC patients, which negative impact on their overall survival [13]. Surgical resection could be considered for solitary hepatic metastasis from lung cancer, although the resectability is limited [14], because selected patients with localized metastasis in the liver, lung or adrenal gland may benefit from aggressive metastectomy. In addition to surgery, radiofrequency ablation and radioembolisation are available for intermediate staged HCC patients, providing preserved liver function and Eastern Cooperative Oncology Group (ECOG) performance status of 0~2, in addition, kinase inhibitor sorafenib is recommended for advanced-stage patients [15]. Transarterial chemoembolization (TACE) is effective to control the growth of pulmonary metastasis which is originated from HCC [16]. However, nearly one-third of these patients do not meet the managements because of advanced age or severe comorbidities, therefore, personalized therapy is warranted beyond the available guidelines [17], as an example, concurrent hepatic arterial infusion floxuridine and systemic administration of capebina plus oxaliplatinum (XELOX) are effective for unresectable liver metastases [18].

Furthermore, the lung is the most common site for extrahepatic metastasis from HCC [19, 20], and resection of pulmonary metastasis may improve survival for selected patients. In addition to surgery, radiotherapy, radiofrequency and microwave ablation of pulmonary metastases are therapeutic options.

It is noteworthy that tumor size is not the indicator of tumor origin. As shown in the latter two cases, the hepatic lesions are larger than the isolated pulmonary lesions, respectively. However, both patients are confirmed pathologically as primary lung cancer with hepatic metastasis. Besides, if the initial therapy is not effective, simultaneous biopsy of the distant lesion should be performed for certification of precise diagnosis.

In summary, accurate diagnosis and staging of synchronous primary tumors of different origins are essential for appropriate and timely treatment, therefore, biopsy should be performed separately for different masses to diminish empirical misdiagnosis.

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Disclosure of conflict of interest

None.

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References

[1] Rovatti M, Gerosa E, Turi V, D'Abrosca F and De Cesare F. [Multiple primary malignant neoplasms]. Minerva Chir 1995; 50: 949-958.

[2] Irimie A, Achimas-Cadariu P, Burz C and Puscas E. Multiple primary malignancies--epidemiological analysis at a single tertiary institution. J Gastrointestin Liver Dis 2010; 19: 69-73.

[3] Aydiner A, Karadeniz A, Uygun K, Tas S, Tas F, Disci R and Topuz E. Multiple primary neoplasms at a single institution: differences between synchronous and metachronous neoplasms. Am J Clin Oncol 2000; 23: 364-370.

[4] Liu Z, Liu C, Guo W, Li S and Bai O. Clinical analysis of 152 cases of multiple primary malignant tumors in 15,398 patients with malignant tumors. PLoS One 2015; 10: e0125754.

[5] Riihimaki M, Hemminki A, Fallah M, Thomsen H, Sundquist K, Sundquist J and Hemminki K. Metastatic sites and survival in lung cancer. Lung Cancer 2014; 86: 78-84.

[6] Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, Han JK and Choi BI. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. Radiology 2015; 275: 97-109.

[7] Lin CY, Chen JH, Liang JA, Lin CC, Jeng LB and Kao CH. 18F-FDG PET or PET/CT for detecting extrahepatic metastases or recurrent hepatocellular carcinoma: a systematic review and meta-analysis. Eur J Radiol 2012; 81: 2417-2422.

[8] Wong RJ, Ahmed A and Gish RG. Elevated alpha-fetoprotein: differential diagnosis - hepatocellular carcinoma and other disorders. Clin Liver Dis 2015; 19: 309-323.
[9] Ba MC, Long H, Tang YQ and Cui SZ. GP73 expression and its significance in the diagnosis of hepatocellular carcinoma: a review. Int J Clin Exp Pathol 2012; 5: 874-881.
[10] Santarpia M, Karachaliou N, Gonzalez-Cao M, Altavilla G, Giovannetti E and Rosell R. Feasibility of cell-free circulating tumor DNA testing for lung cancer. Biomark Med 2016; 10: 417-430.
[11] Lianidou ES, Markou A and Strati A. The role of CTCs as tumor biomarkers. Adv Exp Med Biol 2015; 867: 341-367.
[12] Klempner SJ, Ou SH, Costa DB, VanderLaan PA, Sanford EM, Schrock A, Gay L, Ali SM and Miller VA. The clinical use of genomic profiling to distinguish intrapulmonary metastases from synchronous primaries in non-small-cell lung cancer: a mini-review. Clin Lung Cancer 2015; 16: 334-339, e331.
[13] Castanon E, Rolfo C, Vinal D, Lopez I, Fusco JP, Santisteban M, Martin P, Zubiri L, Echeveste JI and Gil-Bazo I. Impact of epidermal growth factor receptor (EGFR) activating mutations and their targeted treatment in the prognosis of stage IV non-small cell lung cancer (NSCLC) patients harboring liver metastasis. J Transl Med 2015; 13: 257.
[14] Ueda J, Yoshida H, Mamada Y, Taniai N, Mineta S, Yoshioka M, Kawano Y, Furuki H, Koizumi K and Uchida E. Surgical resection of solitary metastatic liver tumor arising from lung cancer: a case series. Hepatogastroenterology 2012; 59: 2307-2309.
[15] Bruix J, Reig M and Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 2016; 150: 835-853.
[16] Wu H, Zhao W, Liu S, Zheng J, Ji G and Xie Y. Pure transcatheter arterial chemoembolization therapy for intrahepatic tumors causes a shrink in pulmonary metastases of hepatocellular carcinoma. Int J Clin Exp Med 2015; 8: 1035-1042.
[17] Sangiovanni A and Colombo M. Treatment of hepatocellular carcinoma: beyond international guidelines. Liver Int 2016; 36 Suppl 1: 124-129.
[18] Shi L, Zhao J, Lu Q, Chen X, Wang H, Jiang Y, Wu J, Ji M, Xu B, Chen L, Jiang J and Wu C. Initial hepatic artery infusion and systemic chemotherapy for asymptomatic colorectal cancer with un-resectable liver metastasis. Int J Clin Exp Med 2015; 8: 1000-1008.
[19] Kitano K, Murayama T, Sakamoto M, Nagayama K, Ueno K, Murakawa T and Nakajima J. Outcome and survival analysis of pulmonary metastasectomy for hepatocellular carcinoma. Eur J Cardiothorac Surg 2012; 41: 376-382.
[20] Ohba T, Yano T, Yoshida T, Kawano D, Tsukamoto S, Shoji F, Taketomi A, Saitsu H, Takeo S and Maehara Y. Results of a surgical resection of pulmonary metastasis from hepatocellular carcinoma: prognostic impact of the preoperative serum alpha-fetoprotein level. Surg Today 2012; 42: 526-531.