

## CASE REPORT

# Spontaneous regression of a large hepatocellular carcinoma with skull metastasis

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**Abstract** Spontaneous regression of hepatocellular carcinoma (HCC) is a rare phenomenon. This case of a 65-year-old Korean man with HCC and metastatic frontal bone mass that regressed after radiotherapy for frontal bone mass without any other therapeutic modalities is described. The clinical diagnosis of HCC was made because of the presence of a liver mass on abdominal computed tomography (CT) scan, high serum  $\alpha$ -fetoprotein value and tissue diagnosis on frontal bone biopsy. The patient refused any other recommended treatments, but accepted the radiation therapy due to a painful frontal bone mass, and ingested mushroom called *Phellinus linteus* for one and a half years. Ten months after radiation therapy, he experienced a reduction in size of the frontal bone mass and improvement of lesions in the liver, sternum and ribs. The patient is alive and in good condition without any symptoms or tumor aggravation in August 2002. It was concluded that a rare case of spontaneous regression of HCC had occurred.

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**Key words:** hepatocellular carcinoma, *Phellinus linteus*, skull metastasis, spontaneous regression.

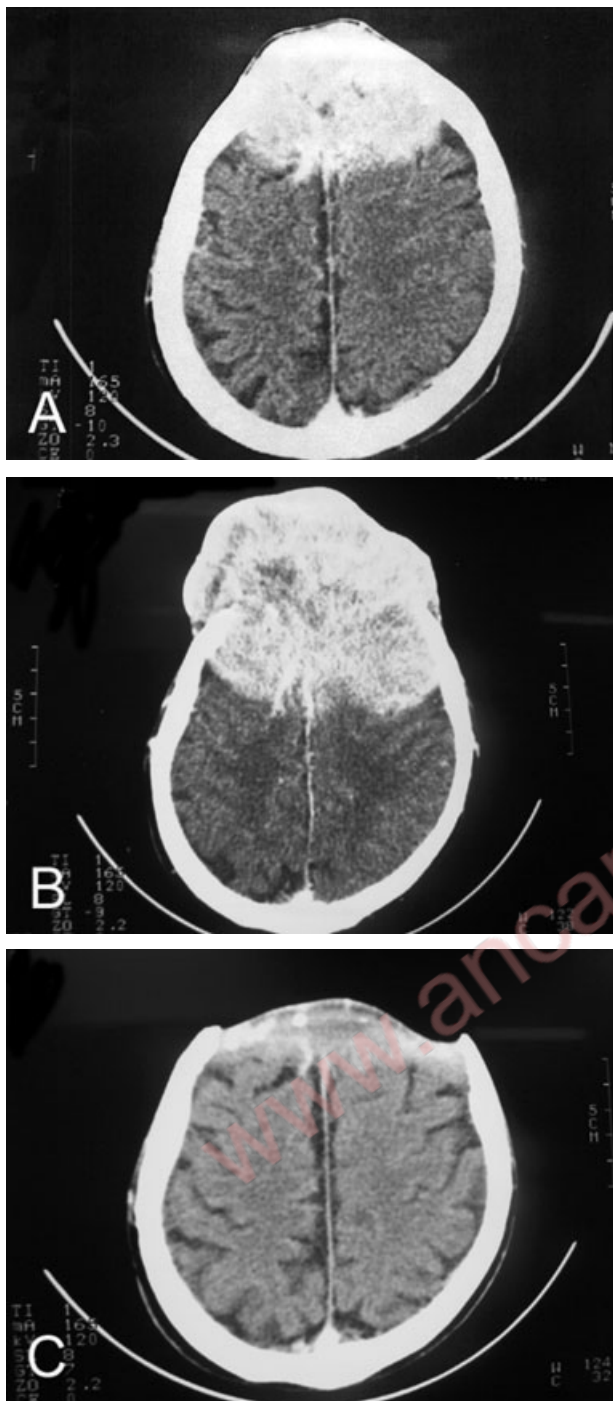
## INTRODUCTION

Primary hepatocellular carcinoma (HCC) is one of the most common and principal cancers worldwide.<sup>1</sup> The occurrence of HCC is primarily associated with chronic viral hepatitis type B and C, which are common causes of hepatic cirrhosis.<sup>2</sup> Without treatment, HCC is usually fatal within a few months. Despite the advances in the diagnosis and treatment modalities or techniques, the long-term prognosis of advanced HCC is still poor.<sup>3</sup> Spontaneous regression of HCC is an extremely rare phenomenon, and the underlying cause of this remission remains obscure. Here, we report a patient who had a spontaneous regression of HCC with skull metastasis with no treatment performed.

## CASE REPORT

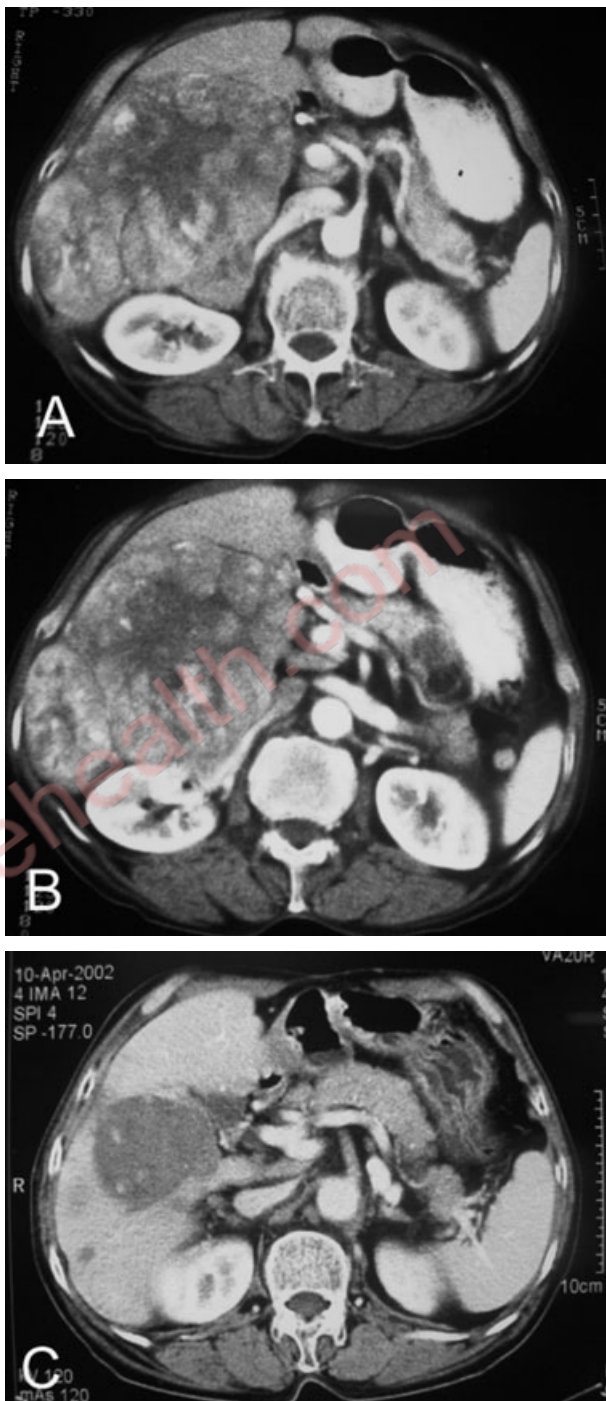
A 65-year-old Korean man was admitted to St Mary's Hospital in Seoul, Korea in June 2000 complaining of a

frontal mass for 1 year. He reported that the frontal mass had grown larger over the previous 6 months. He had no family and past history. The patient had consumed approximately 100 g of alcohol per day for 30 years. On admission, physical examination disclosed a huge, hard and unmovable frontal mass of skull, and abdominal palpation showed that the liver edge was palpable about 5 cm below the right costal margin of the rib cage. Laboratory examination revealed mild hepatic dysfunction. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 78 and 83 U/L, respectively, and the alkaline phosphatase level was 713 U/L. Assays for HBsAg and HBsAb were all negative, but an anti-HCV Ab test was positive. Serum  $\alpha$ -fetoprotein was remarkably elevated above 1200 ng/mL. Computed tomography (CT) of the skull showed a huge, bulging mass of the frontal skull (Fig. 1a). Ultrasonography and CT of the liver showed a multinodular, huge mass of the nearly entire right lobe of the liver (Fig. 2a). Whole body bone scan disclosed the multiple metastasis not only in the hot uptakes of the frontal skull region but also in the 3–5 and 6th ribs and ster-



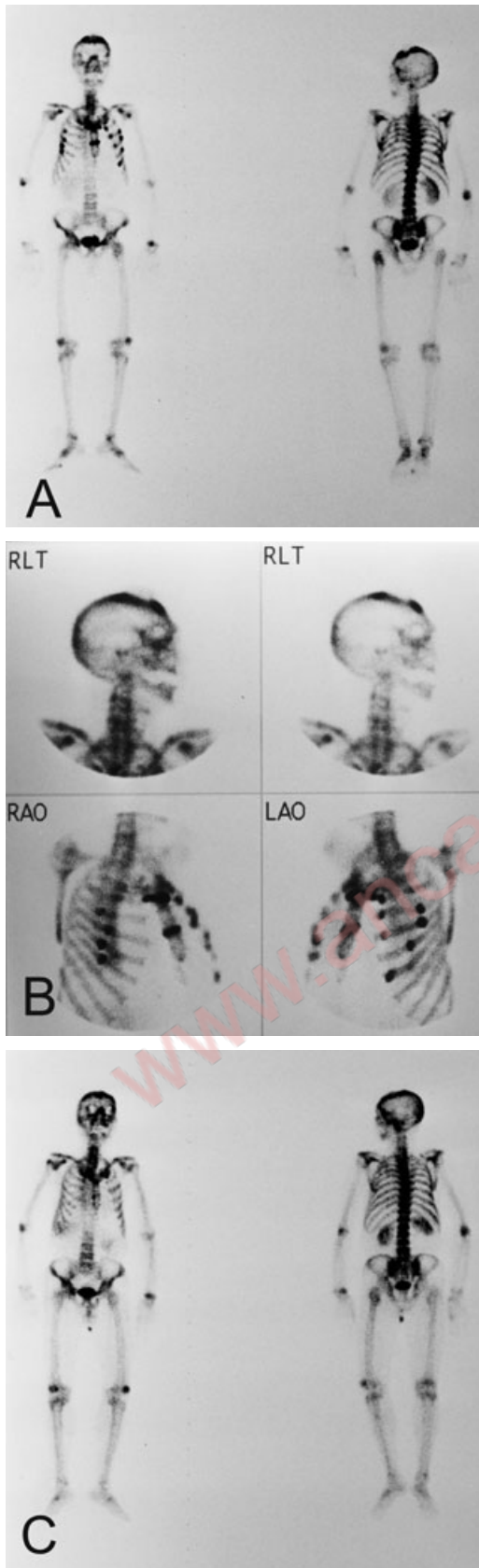
**Figure 1** Brain computed tomography (CT) shows (a) 7 × 1.5 cm sized homogenous enhancement with osteolytic bone defect (October 2000); (b) more aggravated 11 × 10 cm sized large lobulated mass (June 2001) and (c) decreased mass size (April 2002).

num (Fig. 3a,b). Ultrasonography guided liver biopsy was performed and the pathology report showed chronic active hepatitis with a histological activity index (HAI by Knodell) score of 8 (Fig. 4a,b). A biopsy of the



**Figure 2** Abdomen computed tomography (CT) shows (a) huge, heterogenous, hypodense mass involving nearly the total right lobe. Multiple small daughter nodules are also seen at the anterior portion of the right lobe and the medial segment of the left lobe (October 2000); (b) more extensive hepatocellular carcinoma (HCC) involving whole liver (August 2001); and (c) significant regression of HCC mass lesion (May 2002).

frontal skull mass was also carried out and the pathology department reported a metastatic HCC (Fig. 4c,d). The patient refused all recommended treatment modalities and was discharged. After discharge, he ingested a

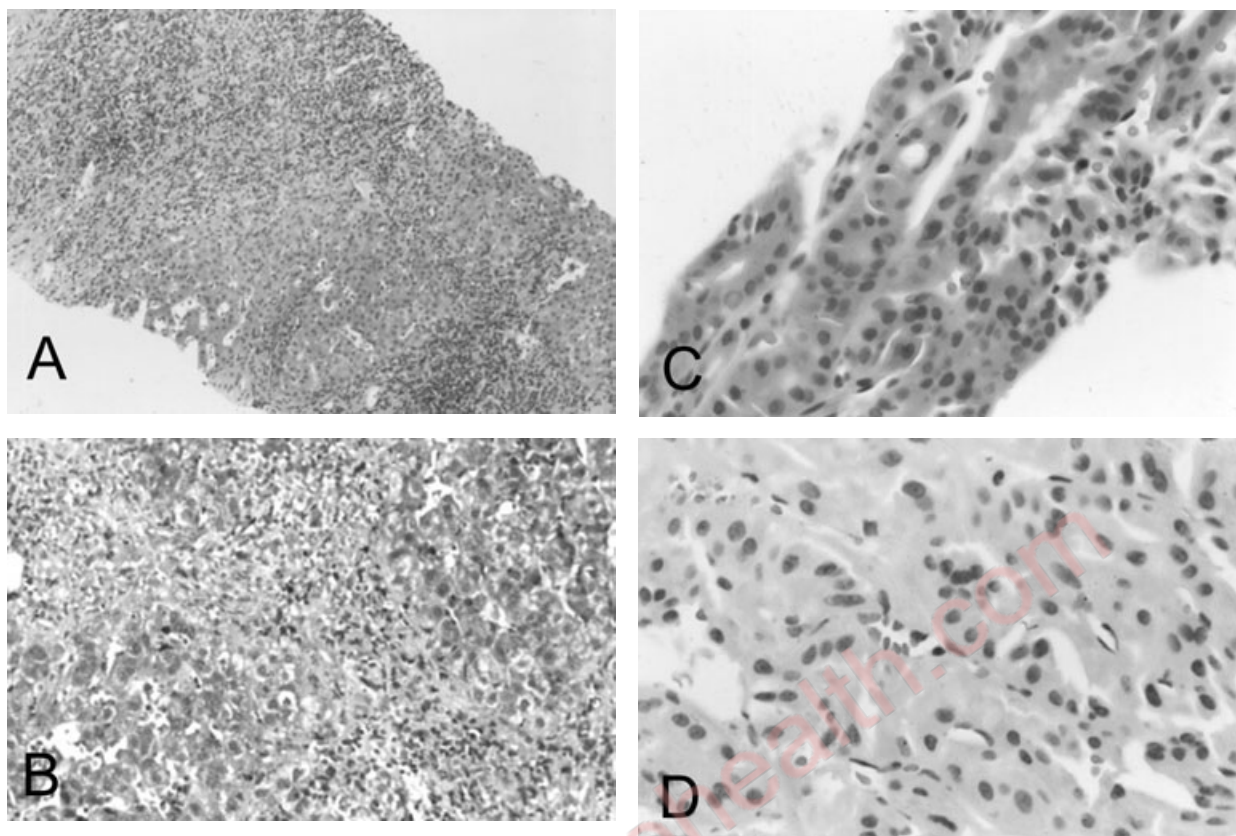


mushroom called *Agaricus (Phellinus linteus)* for 18 months. One month after discharge, he agreed to have the radiation therapy applied to the frontal skull mass because of the resulting headache. During the 2 weeks of a radiation therapy schedule, he was radiated with approximately 3000cGy radiation to the skull lesion. Two months after radiation therapy, the follow up of the abdomen CT showed more aggravation of the lesions in the liver (Fig. 2b), and the size of the frontal skull mass was slowly growing (Fig. 3b). Ten months after radiation therapy, the follow-up CT revealed a marked reduction in the size of the hepatic mass and a reduction in the number of nodules. In addition, a follow up whole body bone scan also showed an absence of the previous hot uptakes of the ribs, sternum and a reduced uptake of the skull lesion (Fig. 3c). The patient reported that the size of the frontal skull mass was much smaller and that he felt well. After 3 months of this regression episode, the follow up CT showed additional degradation in the size and number of nodules of the lesion, and the skull mass had disappeared completely (Fig. 1c). After 9 months of the episode, an additional abdomen CT examination showed even more regression of the prior hepatic lesions (Fig. 2c). Up to now, he reported feeling well and that there was no further growth of the skull mass. Laboratory findings showed a normalized liver function, and the serially checked  $\alpha$ -fetoprotein level showed a decrease to the normal range (Fig. 5). The patient was still alive and in good condition without any symptoms or tumor aggravation in August 2002.

## DISCUSSION

Hepatocellular carcinoma is the third most common cancer in the world and the incidence is particularly high in South Africa and Asia.<sup>4</sup> Metastases of HCC has not yet received much attention because the initial clinical findings that manifest as symptomatic metastases are not frequent.<sup>5</sup> Once metastasis occurs, the availability of treatment is narrowed and the prognosis is poorer than with non-metastatic HCC. A metastasis of this highly vascular malignancy is frequently toward the vascular associated organs, and bone involvement is less common than in the other organs. The most common metastasis site of the bone is the vertebra. Therefore, chronic back pain is sometimes associated with a tumor in a few unfortunate patients. The other areas affected can be the pelvis and/or ribs, but skull involvement is rare.<sup>6</sup> Hepatitis B and C virus is known as the principal cause with other minor causes being alcohol and aflatoxin.<sup>7-9</sup> Our patient's data from this case correspond with other reports that the cause of the HCC was hepatitis C virus infection. A spontaneous regression was termed by Everson and Cole in 1990 as a partial or

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**Figure 3** Bone scan shows (a) the intense hot uptake at the frontal and parietal bone (October 2000). (b) Multiple hot foci of 3, 4, 5 and 6th ribs and band-like hot area at the manubrium (October 2000). (c) Follow up bone scan shows much regressed multiple bony metastatic lesions (November 2001).



**Figure 4** Liver biopsy shows mild lobular activity, mild periportal activity, mild intralobular degeneration and septal fibrosis consistent with chronic active hepatitis (A:  $\times 40$ , B:  $\times 200$ ). Frontal lobe of brain biopsy shows metastatic hepatocellular carcinoma (C:  $\times 200$ , D:  $\times 400$ ) in October 2000.



**Figure 5** Graph shows the time course of  $\alpha$ -fetoprotein laboratory values of the patient.

complete involution of a malignant tumor without any specific therapy being applied.<sup>10</sup> Spontaneous regression has been reported in a variety of malignant diseases, including HCC, but malignant melanoma, neuroblastoma and cancer of the kidney are frequent types of tumors presenting this phenomenon.<sup>11</sup> The distinct pathogenesis of the spontaneous regression in malignant tumors is still unclear as there is no consensus due to rare occurrence. However, immunological associations may play the most important role in this phenomenon.<sup>12-14</sup> Many cases reported a regression of a

mass after severe infections,<sup>15,16</sup> a hepatic vessel thrombosis event,<sup>17</sup> and one unique case showed an improvement in the disease after radiation therapy to the mass itself and revealed the inflammatory cytokine TNF- $\alpha$  elevated before and after radiation therapy.<sup>18</sup> Furthermore, a few authors have insisted no causing events or involvement of any treatment modalities.<sup>19</sup> In our case, the diagnosis of HCC was verified by an elevated AFP titer, by the imaging modalities such as ultrasonography and CT, and by the pathologic confirmation of a bone biopsy. The findings obtained 1 month after radiation showed a growing mass and aggravation of the symptoms. The patient was treated with radiation therapy to the skull lesion and experienced a reduction in the mass in both the skull and liver lesions 10 months after radiation therapy. This episode appears to be less associated with the radiation effect. However, the immunological impact of radiation may have some influence on at least some part of the mechanisms of tumor regression. *Phellinus linteus* is a mushroom called *Agaricus*, and has been investigated by many investigators as a possible antitumor agent.<sup>20-23</sup> The patient ingested this mushroom for a long period, but a definite correlation with tumor regression is not known. Unfortunately, we did not obtain blood samples for an immunological evaluation because there was no expectation of tumor regression at that time. Therefore, data explaining the precise immu-

nological association is absent. Although this individual case cannot prove the mechanisms responsible for the spontaneous regression of the HCC, several probable processes may have occurred in this patient. Those hypotheses are that, first, a rapid expansion of the hepatic and skull masses induced necrosis of the tumors or a portal vein occlusion. Second, radiation therapy toward the skull mass induced a delayed abscopal phenomenon that reduced the remote original hepatic masses. Third, the ingestion of *Phellinus linteus* and/or radiation therapy may have affected the regression process simultaneously or separately by immunological modulation due to some unknown mechanisms. In conclusion, an improvement in the huge tumor with bone metastasis was observed, and a more precise evaluation is expected in the near future. A later report will disclose the causes and broaden the knowledge regarding this optimizing episode.

## REFERENCES

- Di Bisceglie AM, Rustgi VK, Hoofnagle JH *et al.* NIH conference: Hepatocellular carcinoma. *Ann. Int. Med.* 1988; **108**: 390–401.
- Beasley RP. Hepatitis B virus as the etiologic agent in hepatocellular carcinoma-epidemiologic considerations. *Hepatology* 1982; **73**: 383–94.
- Ramsey WH, Wu GY. Hepatocellular carcinoma: update on diagnosis and treatment. *Dig. Dis. Sci.* 1995; **13**: 81–91.
- Munoz N, Bosch EX. Epidemiology of hepatocellular carcinoma. In: Okuda, K, Ishak, KG, eds. *Neoplasms of the Liver*. Tokyo: Springer-Verlag, 1987; 3–19.
- Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K. Pathology of hepatocellular carcinoma in Japan: 232 consecutive cases autopsied in ten years. *Cancer* 1983; **51**: 863–77.
- Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. *J. Clin. Oncol.* 1991; **9**: 509–24.
- Hodgson HJF. Primary hepatocellular carcinoma: western experience. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract*, vol. 2. Edinburgh: Churchill Livingstone, 1994; 1365–69.
- Makimoto K, Higuchi S. Alcohol consumption as a major risk factor for the rise in liver cancer mortality rates in Japanese men. *Int. J. Epidemiol.* 1999; **28**: 30–4.
- Mori M, Hara M, Wada I *et al.* Prospective study of hepatitis B and C viral infections, cigarette smoking, alcohol consumption and other factors associated with hepatocellular carcinoma risk in Japan. *Am. J. Epidemiol.* 2000; **151**: 131–9.
- Everson TC, Cole WH. *Spontaneous Regression of Cancer*. Philadelphia: WB Saunders, 1990.
- Cole WH. Efforts to explain spontaneous regression of cancer. *J. Surg. Oncol.* 1981; **17**: 201–9.
- Tsukahara A, Seki S, Iiai T. Mouse liver T cells: their change with aging and in comparison with peripheral T cells. *Hepatology* 1997; **26**: 301–9.
- Moroda T, Iiai T, Suzuki S. Autologous killing by a population of intermediate T-cell receptor cells and its NK1.1<sup>+</sup> and NK1.1<sup>-</sup> subsets, using Fas ligand/Fas molecules. *Immunology* 1997; **91**: 219–26.
- Kawamura T, Seki S, Takeda K. Protective effect of NK1.1<sup>+</sup> T cells as well as NK cells against intraperitoneal tumors in mice. *Cell Immunol.* 1999; **193**: 219–25.
- Challis GB, Stam HJ. The spontaneous regression of cancer. A review of cases from 1900 to 1987. *Acta Oncol.* 1990; **29**: 545–50.
- Lam KC, Ho JC, Yeung RT. Spontaneous regression of hepatocellular carcinoma: a case study. *Cancer* 1982; **50**: 332–6.
- Uenishi T, Hirohashi K, Tanaka H, Ikebe T, Kinoshita H. Spontaneous regression of a large hepatocellular carcinoma with portal vein tumor thrombi: report of a case. *Surg. Today Jpn J. Surg.* 2000; **30**: 82–5.
- Ohba K, Omagari K, Nakamura T *et al.* Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis. *Gut* 1998; **43**: 575–7.
- Van Haltaren HK, Salemans JMJI, Peters H, Vreugdenhil G, Drissen WMM. Spontaneous regression of hepatocellular carcinoma. *J. Hepatol.* 1997; **27**: 211–5.
- Han SB, Lee CW, Jeon YJ *et al.* The inhibitory effect of polysaccharides isolated from *Phellinus linteus* on tumor growth and metastasis. *Immunopharmacol.* 1999; **41**: 157–64.
- Rhee YK, Han MJ, Park SY, Kim DH. In vitro and in vivo antitumor activity of the fruit body of *Phellinus linteus*. *Korean J. Food Sci Technol.* 2000; **32**: 477–80.
- Kim HM, Han SB, Oh GT *et al.* Stimulation of humoral and cell mediated immunity by polysaccharide from mushroom *Phellinus linteus*. *Int. J. Immunopharmac.* 1996; **18**: 295–303.
- Takeda Y, Togashi H, Shinzawa H *et al.* Spontaneous regression of hepatocellular carcinoma and review of literature. *J. Gastroenterol. Hepatol.* 2000; **15**: 1079–86.