Management of Bilateral Adrenal Metastases from Hepatocellular Carcinoma: A Case Report

Meng-Hsuan Hsieh, Zu-Yau Lin, Chih-Jen Huang,[1] Ming-Chen Shih,[2] and Wan-Long Chuang
Departments of Internal Medicine, [1]Radiation Oncology, and [2]Radiology, Kaohsiung Medical University Chun-Ho Memorial Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan.

The adrenal glands rarely are an extrahepatic site for metastasis from hepatocellular carcinoma (HCC). Once identified, adrenal metastasis requires aggressive management, due to the risk of rupture and internal hemorrhaging. Disease management of adrenal metastasis from HCC is limited, given the relative lack of available knowledge, and the present report details our efforts in managing bilateral adrenal metastases from HCC. For this patient, we used radiation therapy and transcatheter arterial chemoembolization (TACE). The left adrenal tumor was treated by 3D conformal radiation therapy, following the failure of TACE. The size of the left adrenal tumor decreased and no evidence of recurrence after management was noted. One right adrenal tumor was treated using two sessions of TACE, and the size of the tumor did not decrease. We later observed that the right tumor actually progressively increased in size. The tumor was then treated by 3D conformal radiation therapy (total 5,400 cGy), and the size decreased by 10 mm, 1 month after treatment. The patient's condition was stable and liver function was maintained at early stage liver cirrhosis (Child A). Renal function was maintained within normal ranges after diagnosis of HCC and throughout the entire follow-up period, and no complications secondary to radiation therapy were noted. Our experience may provide useful information in disease management for these patients.

Key Words: hepatocellular carcinoma, extrahepatic metastasis, adrenal gland, radiation therapy, transcatheter arterial chemoembolization
(*Kaohsiung J Med Sci* 2005;21:371–6)

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, with extrahepatic metastasis typically found during disease progression [1,2]. Edmondson and Steiner reported from autopsy findings that the adrenal gland is the second most common site for metastasis, secondary to the lung [3]. Clinically, however, HCC metastasis to the adrenal gland is rare. When adrenal metastasis is observed, it requires aggressive management, due to the risk of rupture and internal hemorrhage. Experience in the management of adrenal metastasis from HCC is limited [4,5], and current practice calls for adrenalectomy as the main treatment option, followed by transcatheter arterial chemoembolization (TACE, Allura Monoplane Angiography System; Philips, Amsterdam, Netherlands) therapy [4,6]. Radiation therapy, with or without the combination of TACE or percutaneous ethanol injection (PEI) therapy, is rarely used [7]. This case report details our experience in the management of bilateral adrenal metastasis from HCC, using radiation therapy and TACE. Such experience may prove useful in the disease management of such patients.

Case Presentation

In March 1995, a 57-year-old male with liver cirrhosis secondary to hepatitis C was diagnosed with a single nodule of HCC. The nodule, which measured 20 mm in diameter, was not surgically resected, given his persistently elevated alanine transferase (ALT) titer (150–200 IU/L). This level

Received: May 4, 2004 Accepted: March 8, 2005
Address correspondence and reprint requests to: Dr. Zu-Yau Lin, Department of Internal Medicine, Kaohsiung Medical University Chun-Ho Memorial Hospital, 100 Tzyou 1st Road, Kaohsiung 807, Taiwan.
E-mail: monyan@ms14.hinet.net

was considered to reflect active chronic hepatitis (ALT level > 100 IU/L), and the patient was thus considered at risk of progression to severe hepatitis or even hepatic failure, following general anesthesia. Under these circumstances, operative intervention was considered inappropriate and TACE was first performed on August 1, 1995. Following the procedure, the patient received interferon therapy (Welforn 3Mu/tiw) for 24 weeks, as treatment for chronic hepatitis C. The nodule became a hypoechoic lesion with an acoustic shadow and no dominant daughter nodule or mosaic pattern in this hopoechic lesion, after PEI therapy was performed in September 1995.

Unfortunately, during the follow-up period, multiple new HCC nodules were detected and our clinical judgment was that neither PEI nor TACE would be suitable for treating these recurrent nodules. During this period, the patient was asymptomatic. A very large left adrenal tumor measuring 73 mm in diameter was detected during regular follow-up by ultrasound, in October 2002. Comparative abdominal computed tomography (CT) showed not only a very large left adrenal tumor, but also a small right adrenal tumor (Figure 1A). At this time, the masses were still clinically silent, with no detectable symptom or sign (such as hypertension), Cushing syndrome or electrolyte imbalance, which might relate to the abnormal function of the adrenal gland. There was also no abdominal or back pain. TACE for the left adrenal tumor was performed via the left adrenal artery, with Lipiodol 1 mL, and mitomycin 1 mL, followed by the embolizing agent, gelfoam pledget. The effect was very unsatisfactory, given the difficult catheterization of the arteries supplying the tumor (Figure 1B). Through this procedure, the left adrenal tumor was also targeted with 3D-conformal radiation therapy (200 cGy/day, total 5,400 cGy, November to December 2002, by Varian Linear Accelerator 2100CD).

Follow-up angiography performed 1 month after radiation therapy showed marked devascularization of the left adrenal tumor, but a few supplying arteries still remained. Therefore, 3D-conformal radiation was performed again (200 cGy/day, total 4,800 cGy, February to March 2003). After the therapy, there were no detectable gastrointestinal symptoms suggestive of radiation field damage. The size of the left adrenal tumor was reduced to less than 30 mm (Figure 2A) and the follow-up angiography performed in October 2003 showed complete devasculization of the tumor (Figure 2B). No recurrence of left adrenal metastasis has yet to be found.

The right adrenal tumor was also treated by TACE (8 mL Lipiodol ultra-fluid mixed with 50 mg cisplatin, 40 mg epirubicin and 6 mg mitomycin C, followed by embolization with gelfoam pledget, via right adrenal artery). Follow-up CT performed 1 month after TACE showed complete filling of Lipiodol ultra-fluid within the right adrenal tumor. However, the right adrenal tumor did not reduce significantly in size and progressively enlarged soon after

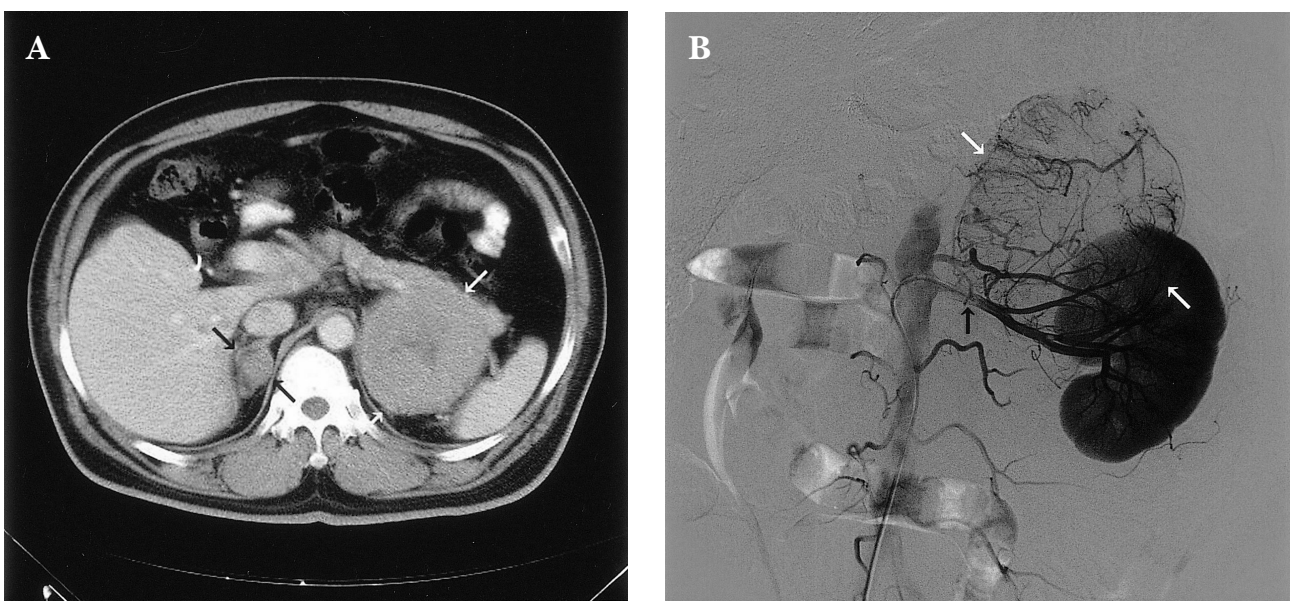

Figure 1. *(A) Contrast-enhanced computed tomography shows a very large left adrenal tumor (white arrow) and a small right adrenal tumor (black arrows). (B) Angiography shows a hypervascular left adrenal tumor (white arrows) with multiple supplying arteries originating from the left renal arteries (black arrow).*

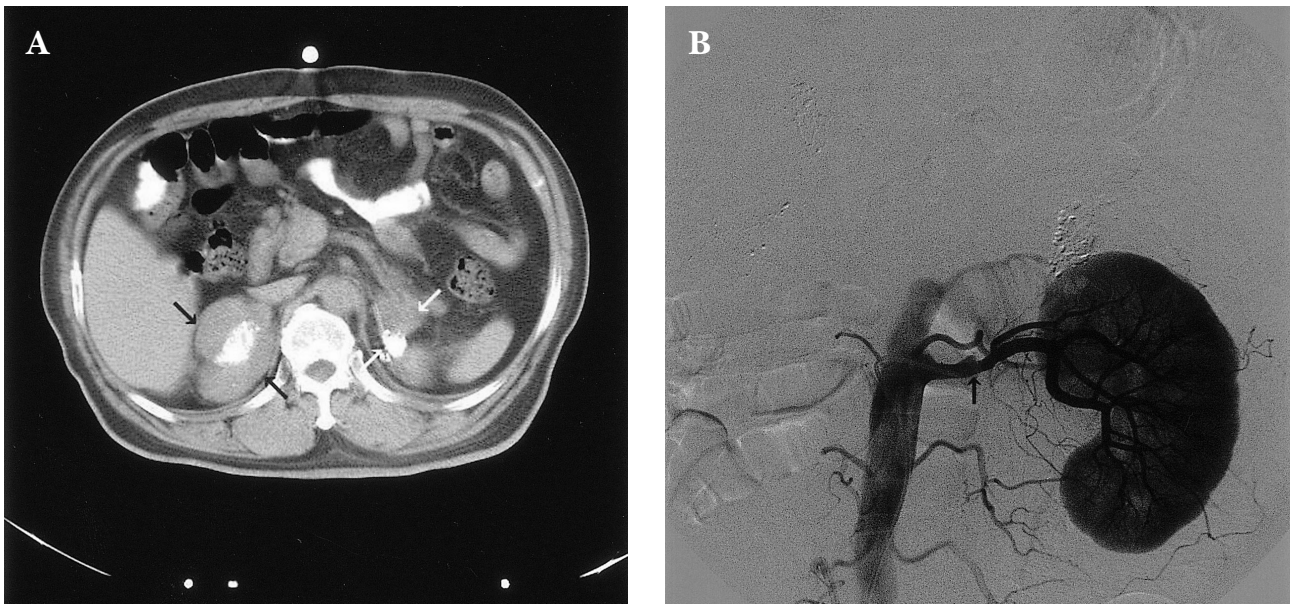

Figure 2. *(A) Contrast-enhanced computed tomography shows the size of the left adrenal tumor (white arrows) decreased significantly to less than 30 mm. The size of the right adrenal tumor (black arrows) increased significantly. The Lipiodol was compressed to the center of the tumor by the cancer cells that had recurred. (B) Angiography shows complete devascularization of the left adrenal tumor (the black arrow indicates the left renal artery).*

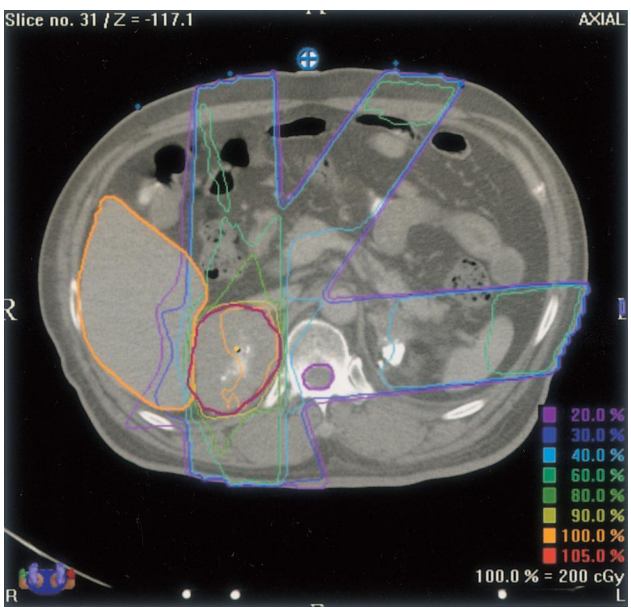

Figure 3A. *Isodose of radiotherapy for the right adrenal tumor, showing the dosage distribution of the energy of 3D-conformal radiotherapy.*

TACE (Figure 2A). The second cycle of TACE for the right adrenal tumor was performed in October 2003 (10 mL Lipiodol ultra-fluid mixed with 30 mg epirubicin and 6 mg mitomycin C, followed by embolization with gelfoam particles). A post-embolized abdominal echo revealed incomplete filling of the Lipiodol ultra-fluid within the tumor, and the patient was then additionally offered 3D conformal radiation therapy to the right adrenal tumor (200 cGy/day, total 5,400 cGy, December 2003 to January 2004) (Figure 3).

No detectable complication for radiation therapy was found. The right adrenal tumor was estimated by ultrasound at 1 month after radiation therapy to have reduced in size by 10 mm, the patient has yet to present evidence of pulmonary or bony metastasis, and the intrahepatic HCC tumors were well controlled by PEI and TACE. The patient's condition remains stable, and the liver function has been maintained at a Child A status (early stage for liver cirrhosis) [8]. The serum alpha-fetoprotein, blood urea nitrogen, and serum creatinine levels have since been maintained within normal ranges, post diagnosis of HCC and for the entire follow-up period.

Discussion

The incidence of adrenal metastasis from HCC at autopsy ranges from 5% to 11% [3]. The route for metastasis is considered hematogenous, but there is also a possibility of direct invasion [9]. Adrenal metastasis is often asymptomatic, unless progressive enlargement of the tumor

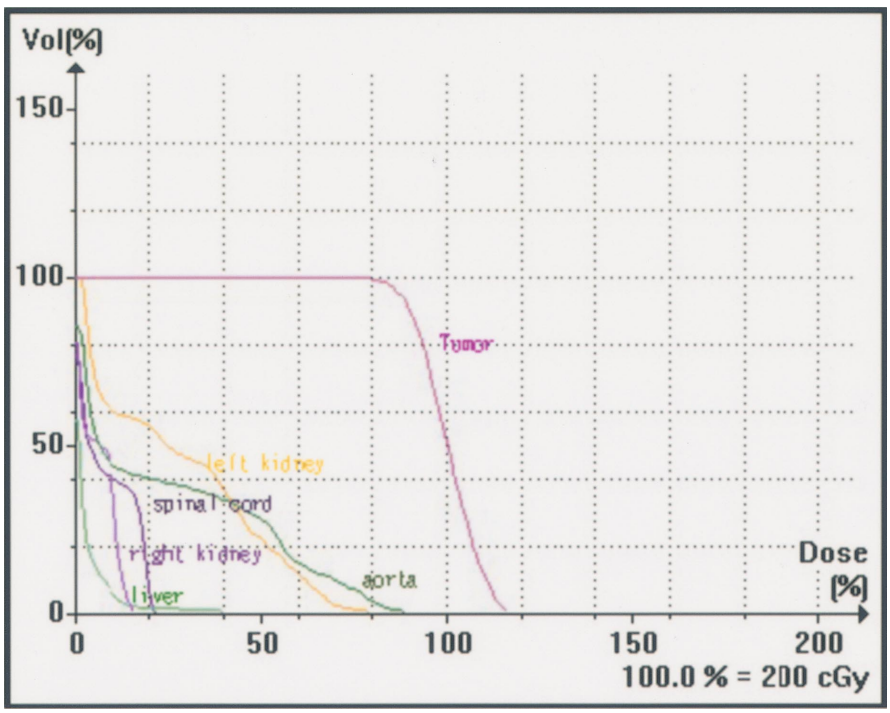

Figure 3B. *Dose volume histograms of the 3D-conformal radiotherapy for the right adrenal tumor.*

is such that compressive symptoms are generated [10]. This metastasis is usually detected by imaging studies during regular follow-up of patients.

In this case report, surgery could not be offered because of the presence of active chronic hepatitis C. The left adrenal tumor was first detected by ultrasound when it was 73 mm in size, and the right adrenal tumor was undetectable by ultrasound. The patient had been regularly followed by ultrasound at intervals of 2–3 months. The sudden appearance of a very large left adrenal tumor may have been due to a rapid growth of the tumor. At the time, the patient did not complain of any specific symptoms. Ultrasound, it should be noted, is a limited scanning method when surveying the adrenal gland. This limitation comes from the gland's location and the frequent interference by intestinal gas.

Moreover, a biopsy of the adrenal mass was not performed because of a difficult approach due to interference from an enlarged spleen and small bowel, hypervascularity of the adrenal mass, and the patient's unwillingness. CT scans are more sensitive than ultrasound in the examination of adrenal gland, because CT is not interfered with by bowel gas and is more sensitive to deep lesions, particularly in the retroperitoneal organs.

Adrenalectomy may cure adrenal metastasis of HCC, but this treatment method carries the risks inherent in such operations. Moreover, Momoi and Shimahara have reported no significant difference in survival between patients treated by adrenalectomy and those by TACE or PEI [4]. In their report, however, the sample number was small and requires validation. In this case, adrenalectomy was not performed, as metastases were present bilaterally, and the patient's previous cardiovascular history augmented the significant morbidity and mortality risks associated with the procedure.

TACE may be effective in the palliative management of adrenal metastasis [4,6]. Essentially, the success of TACE therapy relies on the ability to approach and embolize the whole of the artery supplying the tumor. This is the reason why the left adrenal tumor in the present case report could not be satisfactorily treated by TACE. Another determinant factor for successful TACE therapy is the cancer cells' sensitivity to the anticancer drugs. The intrahepatic HCC tumors in the present case could be successfully controlled by TACE with the same anticancer drugs for adrenal metastasis. Therefore, recurrence of right adrenal tumor after TACE was considered a result from failure to detect some of the very small supplying arteries on angiography for embolization. For this patient, given the difficulty with catheterization, the effectiveness of TACE was not maximal.

Radiation therapy for adrenal metastasis, for its part, carries the risk of damaging the adjacent organs. For the treated patient in our report, the total radiation dose for the left adrenal tumor was extremely high. Nevertheless, there were no detectable complications, because we used 3D conformal radiation with multi-left collimator to protect adjacent organs

such as the liver, kidney, and spinal cord. In addition, the location of the left adrenal tumor was precisely located by ultrasound before 3D conformal radiation therapy, and the dose was divided into 65% from posterior projection and 35% from anterior projection. In this instance, this procedure may have helped reduce unwanted damage to the gastrointestinal system, kidney and spinal cord. Moreover, the application of 3D-conformal radiation therapy may have further reduced the possibility of damage to the adjacent organs.

The right adrenal tumor was not initially treated with radiation therapy, as the large left adrenal tumor was the main priority. Three-dimensional conformal radiation therapy was, however, eventually applied to the right adrenal tumor as well, due to the rapid recurrence of tumor after TACE. The initial result from the radiation therapy was satisfactory. There was no significant influence of radiation on liver and renal function, as the target was precisely located by ultrasound before radiation. It should be noted, however, that the patient is still being monitored, as the symptoms associated with radiotherapy may only appear after a year or longer. Following the interventions detailed above, no aberrant renal or liver functions manifested, and no special symptoms, such as those suggestive of hyperaldosteronism or hypoaldosteronism (Cushing's or Addison's syndrome), were found.

In conclusion, this case report details a satisfactory effect of radiation therapy for the treatment of adrenal metastasis from HCC. The complication of radiation can be minimized by precise location of the target.

References

1. Maki A, Takayatsu T, Mori K, et al. Studies on multidisciplinary therapy for recurrent hepatocellular carcinoma after hepatic resection. *Jpn J Gastroenterol Surg* 1989;22:779–82.
2. Castroagudin JF, Gonzalez-Quintela A, Martinez J, et al. Bilateral adrenal metastasis from hepatocellular carcinoma after liver transplantation. *Hepatogastroenterology* 2002;49:249–51.
3. Edmondson HA, Steiner PE. Primary carcinoma of the liver – a study of 100 cases among 48,900 necropsies. *Cancer* 1954;7: 462–503.
4. Momoi H, Shimahara Y. Management of adrenal metastasis from hepatocellular carcinoma. *Surg Today* 2002;32:1035–41.
5. Inagaki Y, Unoura M, Urabe T, et al. Distant metastasis of hepatocellular carcinoma after successful treatment of the primary lesion. *Hepatogastroenterology* 1993;40:316–9.
6. Taniai N, Egami K, Wada M, et al. Adrenal metastasis from hepatocellular carcinoma (HCC): report of 3 cases. *Hepatogastroenterology* 1999;46:2523–8.
7. Takada K, Nakamura K, Usuki N, et al. Adrenal arterial embolization and radiotherapy of a case with metastatic adrenal tumor and its tumor thrombus in inferior vena cava from hepatocellular carcinoma. *Jpn J Clin Radiol* 1989;34:1529–32.
8. Green GB, Harris IS, Lin GA, et al. Table 17–5. In: *The Washington Manual of Medical Therapeutics*. Philadelphia: Lippincott Williams & Wilkins, 2004:397.
9. Okuda K, Arakawa M, Kubo Y, et al. Right-sided pedunculated hepatocellular carcinoma: a form of adrenal metastasis. *Hepatology* 1998;27:81–5.
10. Kuromatsu R, Hirai K, Majima Y, et al. A patient with hepatocellular carcinoma who underwent resection of the primary lesion 10 years ago and resection of a giant adrenal metastasis 8 and a half years later. *Gastroenterol Jpn* 1993;28: 312–6.

兩側腎上腺肝癌轉移之治療經驗 — 病例報告

謝孟軒[1] 林子堯[1] 黃志仁[2] 石明誠[3] 莊萬龍[1]

高雄醫學大學附設中和紀念醫院 [1]肝膽胰內科 [2]放射治療科 [3]放射線科

腎上腺是肝癌肝外轉移在臨床上比較少見受侵犯之器官，由於腎上腺之肝癌轉移瘤有破裂出血之危機，因此在治療上需採取積極之治療。目前在腎上腺肝癌轉移之治療經驗仍很缺乏，本病例報告提供一位有兩側腎上腺肝癌轉移之病患，經放射治療及經導管動脈化學栓塞治療之經驗，患者左側腎上腺肝癌轉移瘤因經導管動脈化學栓塞治療失敗，故採取3D-conformal放射治療，治療後腫瘤縮小，且於追蹤期間無復發之證據，其右側腎上腺肝癌轉移瘤接受兩次經導管動脈化學栓塞治療，但腫瘤在治療後並無明顯縮小，反而逐漸變大，故又接受3D-conformal放射治療(共5,400cGy)，腫瘤於治療後一個月縮小1公分，患者之肝功能維持在 Child A 等級、腎功能於追蹤期間均維持正常，患者也無出現明顯可查覺之放射治療副作用，我們之經驗可提供往後處理類似患者之參考。

關鍵詞：肝細胞癌，肝外轉移，腎上腺，放射治療，經導管動脈化學栓塞治療

（高雄醫誌 2005;21:371—6）

收文日期：93 年 5 月 4 日

接受刊載：94 年 3 月 8 日

通訊作者：林子堯醫師

高雄醫學大學附設中和紀念醫院肝膽胰內科

高雄市三民區自由一路100號