

POTENTIAL EFFICACY OF ALLERGEN REMOVED *Rhus Verniciflua* Stokes Extract TO MAINTAIN PROGRESSION-FREE SURVIVAL OF PATIENTS WITH ADVANCED HEPATOBILIARY CANCER

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Hepatobiliary cancers are among the leading causes of cancer-related deaths worldwide. Most of the early-stage, surgically resectable cases show recurrence, and when they do, the prognosis is dismal with limited available treatment options.

Here, we report three patients with relapsed hepatobiliary cancers who presented relatively long progression-free survival with the administration of a natural product, allergen removed *Rhus verniciflua* Stokes (RVS) extract. After commencement of RVS extract, they were progression-free for over 56 months in one case of recurred cholangiocarcinoma, and for over 16 and 114 months respectively, in

two cases of advanced hepatocellular carcinoma. These cases suggest that the RVS extract could be a potential alternative for advanced hepatobiliary cancer that has no other available treatment.

Keywords: Hepatobiliary cancer, Hepatocellular carcinoma, Cholangiocarcinoma, Progression-free survival, *Rhus verniciflua* Stokes, Herbal

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INTRODUCTION

Hepatobiliary cancers are highly aggressive cancers with a poor prognosis. Surgical resection is regarded as the only potentially curative approach for localized disease. Unfortunately, the majority of patients are initially diagnosed with advanced disease; moreover, most of the patients who undergo surgery eventually have recurrence. Hepatobiliary cancers also tend to have poor response to chemotherapy and radiotherapy.¹ Here, we report three cases of hepatobiliary cancers that after relapse of the tumor showed relatively long progression-free survival following treatment with RVS extract.

CASE PRESENTATIONS

Case 1

A woman diagnosed with distal bile duct cancer at 60 years of age, was referred to a university hospital for surgical

management. A Whipple procedure was performed in September 2006, and the size of the tumor was $3.1 \times 1.3 \times 0.5$ cm. The histology revealed poorly differentiated adenocarcinoma with pancreatic invasion; the pathologic stage of IIA (pT3N0M0) was made utilizing the staging system of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC).

On November 2006, about 2 months after the operation, abdominal CT scan showed a newly developed infiltrative soft tissue lesion that was in the inferior aspect of the pancreaticejunostomy site, measuring 2.3 cm and encasing superior mesenteric vein (SMV) and the proximal main portal vein. A course of salvage chemotherapy with 5-fluorouracil followed by regional radiotherapy at a dose of 180 cGy/33fractions was administered. Unfortunately, a follow-up CT scan taken in January 2007 revealed increase in the size of the tumor from 2.3 cm to 3 cm and the development of scanty ascites in the perihepatic space (Fig. 1A). Second-line chemotherapy with gemcitabine and cisplatin was recommended accordingly. However, she refused further therapy and visited the Integrative Cancer Center for second opinion. Initial blood test results were within normal limits except for mild anemia.

Treatment with RVS extract, 500 mg capsule taken twice a day was initiated in March 2007. Three months after initiation of therapy, a follow-up CT scan showed interval decrease in the size of the tumor around the SMV. The CT scan, taken in October 2007, showed further attenuation of the tumor size around the SMV. The dosage of RVS extract was reduced to once a day in October 2007. There was no

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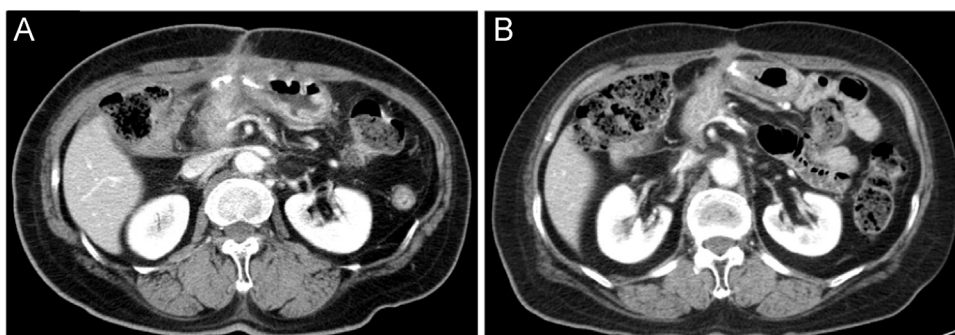


Fig. 1. CT scans of case 1. (A) An abdominopelvic CT scan taken in January 2007 showing recurrent soft tissue mass around the superior mesenteric vein (SMV), which had further increased despite chemoradiotherapy. (B) A follow-up CT scan taken in June 2010, showing no interval change in the attenuated mass around the SMV.

significant interval change in the size of the tumor around the SMV (Fig. 1B) until November 2011, when a newly developed right portal vein thrombosis occurred. In this case of relapsed cholangiocarcinoma, the patient was progression-free for 56 months following the commencement of monotherapy with RVS extract.

Case 2

A 68-year-old man with underlying hepatic cirrhosis and chronic hepatitis C was diagnosed with an unresectable multinodular hepatocellular carcinoma (HCC) on CT in August 2007. The result also showed portal vein thrombosis in the main and intrahepatic portal veins, multiple lymphadenopathies in the peripancreatic, porta hepatis and portocaval spaces, and a moderate amount of ascites. After the failure of transarterial chemoembolization (TACE), radiotherapy was initiated with a dose of 180 cGy/23 fractions. However, a follow-up CT scan showed increased extent of multinodular HCC. In November 2007, the patient visited the Integrative Cancer Center for supportive care. On presentation, the patient's cancer was classified as stage D by Barcelona Clinic Liver Cancer (BCLC) staging with performance status of three by Eastern Cooperative Oncology Group criteria, and the Child-Pugh Score was B without extrahepatic spread (Fig. 2A). The levels of serum bilirubin, albumin, and alpha-fetoprotein (AFP) were 6.0 mg/dL, 3.3 g/dL, and 2040 ng/mL, respectively.

Herbal treatment with a 500 mg capsule of RVS extract once a day was initiated in November 2007 without a concomitant antiviral agent. A follow-up CT scan taken in July 2008 showed equivocal change of the multinodular HCC, but the blood tests showed a marked 122.8 ng/mL decrease in AFP. Serum bilirubin and albumin were also stabilized to 0.9 mg/dL and 4.3 g/dL, respectively. The size of the tumor was reportedly stable (Fig. 2B) until April 2009 when the abdominal CT scan showed slight increase in the size of the hepatic mass. A follow-up CT scan taken in July 2009 revealed further progression. In this case, the progression-free survival was over 16 months since the initiation of RVS extract. It is also notable that the serial serum AFP results showed 94% reduction after RVS treatment (Fig. 4A).

Case 3

A 42-year-old man with a history of hepatitis was diagnosed with single-nodule HCC that was located in segment VI of the liver, and underwent TACE in July 2005. After the procedure, he visited a private hospital that specialized in cancer care. At the time of presentation, BCLC staging was stage B with minimal cancer-related symptoms and serum AFP was 702 ng/mL. Herbal treatment with a 500 mg capsule of RVS once a day without concomitant antiviral agent was started in August 2005.

In September 2007, 26 months after TACE, a PET-CT scan and spine MRI showed a newly developed hypermetabolic lesion in the seventh thoracic vertebra that proved to be metastasis with perivertebral soft tissue involvement (Fig. 3A). Serum AFP concentration was elevated to 4330.8 ng/mL. A higher dose of RVS extract, 500 mg three times a day, was initiated and a thoracic vertebrectomy was performed in December 2007. The biopsied tissue was confirmed to be consistent with metastatic HCC. After the operation, helical tomotherapy to the vertebrae from T5 to T9 was administered at a dose of 250 cGy/20 fractions.

In June 2008, the serum AFP concentration was down to 307.6 ng/dL, and further decreased to 53.2 ng/dL in September 2008. Since June of 2009, considering the stable status of both the tumor and serum AFP concentration, which was down to 10.6 ng/dL, the dosage of RVS extract was reduced to original 500 mg capsule once a day. The latest follow-up was in February 2017, when the MRI revealed no evidence of progression in the liver or vertebra, and the serum AFP concentration was maintained at 7.62 ng/dL (Fig. 3B and C).

Following the combination therapy of vertebrectomy/regional radiotherapy and RVS treatment, the patient has remained progression-free for almost 10 years since the extrahepatic recurrence. Furthermore, after the treatment, there was more than a 99% reduction in serum AFP concentration (Fig. 4B).

DISCUSSION

Hepatobiliary cancers, mainly HCC and cholangiocarcinoma, are high mortality diseases that are often diagnosed late in the disease process.^{2,3} Although there have been major developments in diagnosis and treatment of these tumors, the aggressive behavior, underlying cirrhosis and late presentation

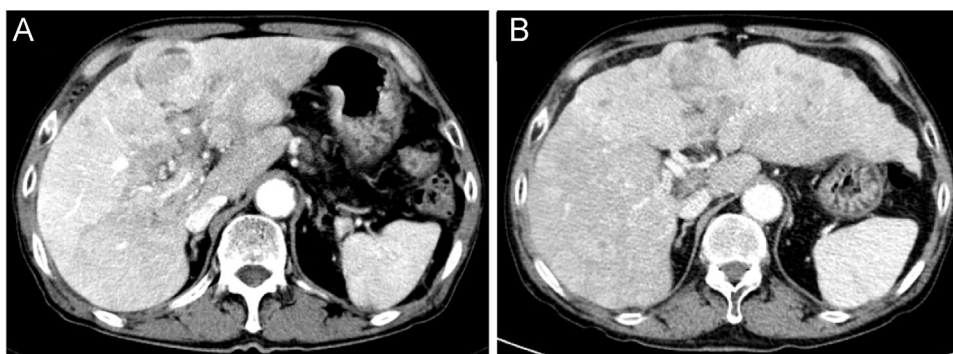


Fig. 2. CT scans of case 2. (A) An abdominal CT scan taken in October 2007, presenting multinodular HCC in both lobes of the liver with marked elevation of serum AFP concentration to 2040 ng/mL. (B) A follow-up CT scan taken in January 2009, about 14 months after the initiation of RVS treatment, showing equivocal change in the multinodular HCC.

still leads to poor clinical outcomes.⁴ At an advanced stage of HCC, the tyrosine kinase inhibitors sorafenib and the recently approved regorafenib are the only available treatment options. Sorafenib is reported to improve overall survival by 3 months, 10.7 months vs. 7.9 months⁵; regorafenib, as a second-line treatment for sorafenib-failed advanced HCC patients, was reported to improve overall survival by 3 months, 10.6 months vs. 7.8 months.⁶ In the case of advanced cholangiocarcinoma, combination therapy of cisplatin plus gemcitabine showed an improved overall survival, 11.7 months vs. 8.1 months.⁷ Despite these advances, the effectiveness of current treatment of hepatobiliary cancer leaves much to be desired, especially in the advanced and refractory stage.

RVS has been used for the treatment of abdominal masses since the 15th century AD in Korea.⁸ Though RVS has anticancer effects, its medical use has been limited by the presence of the toxic allergen, urushiol. For eliminations of urushiol, dried RVS sawdust was extracted twice with 10 times its volume of water at 90–95°C. After concentration and freeze-drying, the RVS extract was analyzed with high-performance liquid chromatography for quality control. The RVS extract was evaluated and standardized with non-detection of urushiol and the contents of major compounds, fustin and fisetin.

The anticancer effect of RVS has been shown, mainly focusing on inhibition of tumor growth and induction of apoptosis, in several experimental studies. In a study of RVS

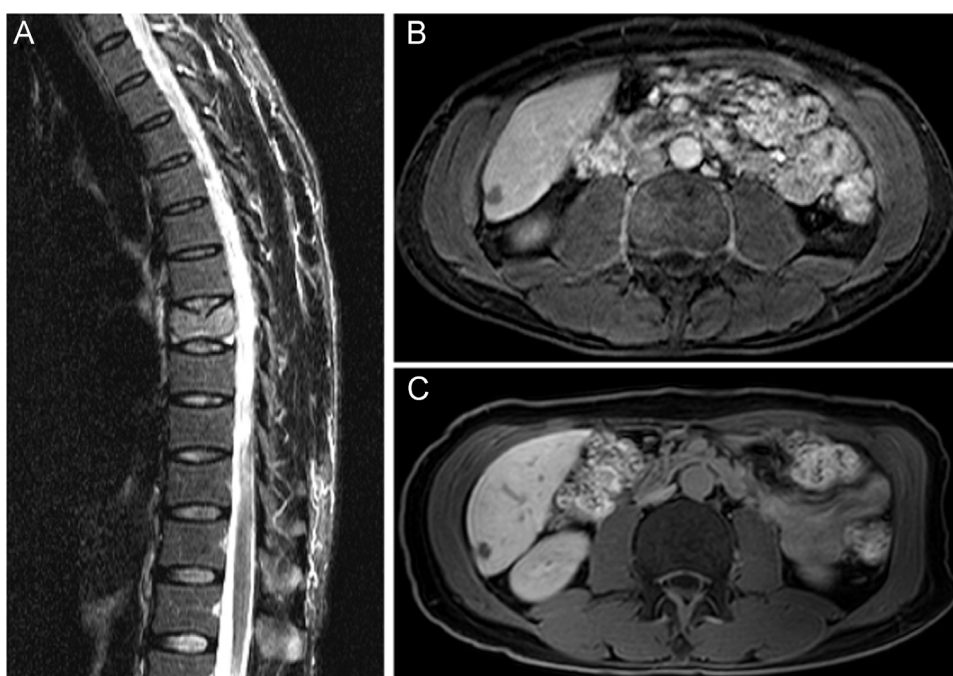


Fig. 3. MRI scans of case 3. Follow-up MRI scans of the previously TACE-treated HCC site in liver S6 showing stable disease, taken in April 2011 (B) and February 2017 (C). (A) Thoracic spine MRI taken in September 2009, showing metastasis in the T7 body with mild degree of pathologic compression fracture.

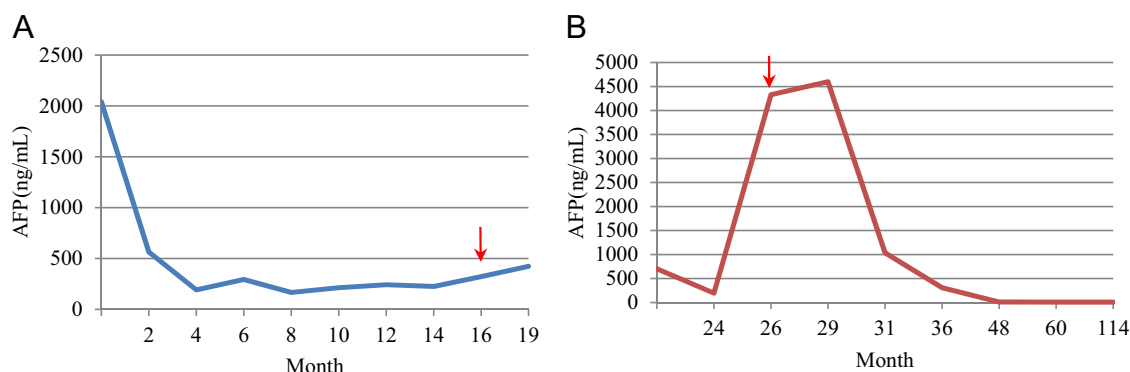


Fig. 4. Serial AFP concentration changes of case 2 and case 3 during the RVS treatment. (A) Serum AFP concentration was markedly decreased within 4 months, but the tumor showed progression after 16 months. (B) Serum AFP had increased up to 4330.8 ng/mL, 26 months after the RVS treatment and 29 months after TACE. The value dropped after the vertebrectomy and RVS dosage adjustment, and is now within normal limits.

on human gastric cancer cells, RVS induced G1 phase cell cycle arrest and inhibited the PI3K-Akt/PKB pathway that enhanced the mitochondrial death pathway.^{9,10} A more recent study has demonstrated that RVS extract down-regulated the TNF- α -mediated NF- κ B pathway to promote JNK activation, which results in apoptosis.¹¹ *In vitro* studies of RVS reported anticancer effects on several other cancer cell types, such as Lewis lung carcinoma (LLC), non-small cell lung cancer (NSCLC), human lymphoma, osteosarcoma, and breast cancer.^{12–16} *In vivo* studies of RVS have reported suppression tumor growth in animal models with A549 cells, LLC, Ca-755 beast carcinoma, and RSHM-5 uterine cervix.^{12,17} The proliferation and migration activity of human umbilical vein endothelial cells was also inhibited by RVS.¹² Reports of an interaction study indicated that RVS combined with cisplatin prevented cisplatin-induced toxicity without influence on the antitumor effect of cisplatin in MDCK-I renal cell and BALB/c mice with CT-26 colon adenocarcinoma.¹⁸

There are also several case studies and clinical studies that have previously reported notable response to RVS treatment in patients with various types of cancer. Two patients with metastatic renal cell carcinoma treated with RVS have achieved disease-free survival of over 31 months and 29 months,¹⁹ and partial response with polypoid mass shrinkage was reported in an elderly patient with gastric adenocarcinoma.²⁰ Another patient with HCC that was refractory to doxorubicin after liver transplantation had an objective response of lung metastasis and progression-free survival of 8 months.²¹ There were two clinical studies investigating the response of RVS treatment in patients with NSCLC. One showed median survival time of 8.4 months and 1-year survival of 40% in 40 patients who had failed first-line or second-line chemotherapy.²² In another study involving 33 patients with non-progressive NSCLC, following first-line chemotherapy, the median progression-free survival was 5.2 months and 1-year survival rate was 84.2%.²³ A series of 12 patients with ampulla of vater cancer showed median overall survival of 15.1 months and progression-free survival of 3 months.²⁴

The three cases presented here are of objective responses and prolonged stable disease in patients with hepatobiliary cancer who were treated with RVS. These cases indicate that RVS can be another option for the management of advanced hepatobiliary cancer that has no available standard regimen.

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