문맥혈전을 동반한 간세포암 환자에서 간동맥화학색전술과 정위방사선치료 후 완전관해 및 담관협착을 보인 사례

임채홍¹ · 임형준² · 정영걸² · 정환훈³ · 서상준² · 윤원섭¹

고려대학교 의과대학 안산병원 ¹방사선종양학과, ²소화기내과, ³영상의학과

A Case of Complete Response with Biliary Stenosis after Hepatic Arterial Injection and Stereotactic Body Radiotherapy to Hepatocellular Carcinoma with Portal Vein Thrombosis

Chai Hong Rim¹, Hyung Joon Im², Young Geol Jung², Hwan Hoon Chung³, Sang Joon Seo², Won Sup Yoon¹

¹Department of Radiation Oncology, ²Division of Gastroenterology, Department of Internal Medicine, and ³Department of Radiology, Ansan Hospital, Korea University College of Medicine, Ansan, Korea

Curative treatment of hepatocellular carcinoma (HCC) with portal vein invasion is difficult to achieve, and the prognosis is dismal. Combining external beam radiotherapy (EBRT) with hepatic arterial infusion chemotherapy (HAIC) has shown favorable local therapeutic effects for patients with HCC exhibiting portal vein invasion. Stereotactic body radiotherapy (SBRT) is a recently developed EBRT modality that shows excellent tumor control. The combination of SBRT and HAIC for HCC with portal vein invasion has not been well-studied. We report a patient with HCC and portal vein invasion who achieved 15 months of survival with complete response status after combination SBRT and HAIC. The patient later experienced grade 3 biliary stricture and died of liver abscesses of unknown etiologies that subsequently appeared. (*J Liver Cancer* 2018;18:75-79)

Keywords: Hepatocellular carcinoma; Stereotactic body radiotherapy; Hepatic arterial infusion chemotherapy; Portal vein

Received Oct. 31, 2017

Revised Jan. 2, 2018

Accepted Jan. 8, 2018

INTRODUCTION

Hepatocellular carcinoma with portal vein invasion is currently classified as stage C according to the Barcelona Liver Cancer Clinic (BCLC) classification; the proposed standard treatment is sorafenib.¹ However, combined treatments in-

cluding local treatment such as external beam radiation therapy (EBRT) are commonly used,² because the tumor response and survival benefit owing to sorafenib alone are unsatisfactory.³ The Asia-Pacific Primary Liver Cancer consensus recommends combined radiotherapy in patients with BCLC stage C tumors.⁴

Transarterial chemoembolization (TACE) and hepatic arterial injection chemotherapy (HAIC) can be used combined with EBRT for HCC with portal vein invasion.^{5,6} Stereotactic body radiotherapy (SBRT) is a novel technique that delivers a high radiation dose to lesions over a short period of time, usually 1–2 weeks. SBRT also treats lesions in major vessels such as the portal vein.⁷ However, grade ≥ 3 biliary toxicities have been reported after SBRT for HCC with portal vein in-

Corresponding author : Won Sup Yoon

Department of Radiation Oncology, Ansan Hospital, Korea University College of Medicine, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea
Tel. +82-31-412-6850, Fax. +82-31-412-6851
E-mail; irionyws@korea.ac.kr
<http://orcid.org/0000-0002-6098-1993>

vasion.^{8,9} We report a patient with HCC exhibiting portal vein invasion who maintained complete response status after SBRT and HAIC; he ultimately died owing to the aggravation of a liver abscess with unknown etiology.

CASE REPORT

1. Clinical presentation

A 67-year-old man experienced upper-right abdominal pain for 3 weeks and was referred from a private clinic after HCC was suspected following computed tomography (CT) and ultrasonography. The patient was unaware of any viral hepatitis history and had not undergone regular screening. He consumed 1.5 bottles of Soju (Korean distilled liquor with an alcohol content of 15–20%) daily until 3 months prior. He also smoked a pack of cigarettes daily for 35 years, and was on medications for hypertension and diabetes. He had undergone an appendectomy 40 years ago.

Blood analyses revealed white blood cells at 12,900/mm³, hemoglobin of 14.7 g/dL, and platelets at 308,000/mm³. Biochemical analyses showed total protein 8.6 g/dL, albumin 4.6 g/dL, blood urea nitrogen 9.4 mg/dL, creatinine 1.08 mg/dL, aspartate aminotransferase/alanine aminotransferase 24/19 IU/L, alkaline phosphatase 103 IU/L, total cholesterol 32 mg/dL, total bilirubin 0.49 mg/dL (direct bilirubin 0.12 mg/dL), and prothrombin time/international normalized ratio 0.99. Viral hepatitis serologic tests showed HBsAg (+), anti-HBs Ab (+), anti-HCV Ab (-), IgG anti-HBc (+), and HBV DNA 232,634 IU/mL. As for tumor markers, alpha-fetoprotein (AFP) was 598.4 ng/mL and protein induced by vitamin K absence-II (PIVKA-II) was 51 mAU/mL.

2. Diagnosis

Primovist magnetic resonance imaging (MRI) showed a 4.7 cm mass with arterial enhancement and delayed washout in segment 6. This lesion formed a tumor thrombus in the main portal vein up to the right 2nd-ordered and left 1st-ordered branches (Fig. 1). Ascites was not evident, and the liver surface was smooth.

At diagnosis, the patient's Child-Pugh score was 5, and he was classified as class A; his Eastern Cooperative Oncology Group performance status score was 1. The tumor was considered BCLC stage C (advanced) owing to portal vein invasion.

3. Treatment and progress

We planned a combination therapy of HAIC and SBRT. HAIC was performed with the following protocol every 4 weeks; 5-FU 750 mg on day 1, 5-FU 750 mg and cisplatin 90 mg on day 2, and 5-FU 750 mg on day 3. For SBRT planning, gross tumor volume (GTV) was drawn using planning CT and 3 minute delayed MRI images, which are fused with rigid registration method. Abdominal compressor was applied at umbilical area to diminish respiratory movement, and internal target volume (ITV) was designed considering the respiratory movement tracked by Real-Time Position Management system (Varian Medical System, Palo Alto, CA). Then, a planning target volume (PTV) was expanded by 3 mm from ITV. We followed the guidelines of Korean Liver Cancer Study Group, having a mean normal liver dose of <28 Gy (in equivalent dose of 2 Gy per fraction), and more than 700 cc of normal liver volume received the dose of <15 Gy.¹⁰ The planned dose of 48 Gy was divided into 4 fractions and delivered to PTV every other day. The duodenum D_{1cc} (the largest dose received by at least 1 cc of duodenum) was 23.5 Gy, and the mean PTV dose was 48.1 Gy. The planning was performed using Eclipse 8.9 (Varian Medical System, Palo Alto, CA). The SBRT plan and dose-volume histogram are shown in Fig. 2.

One month after SBRT and after 2 cycles of HAIC, the longest diameter of the tumor decreased from 4.7 cm to 4 cm, and left portal vein patency was almost fully restored. AFP levels significantly dropped from 598.4 ng/mL to 14.5 ng/mL and normalized. PIVKA-II levels also normalized at 32 mAU/mL. At 7 months post-SBRT and 6 cycles of HAIC, the longest tumor axis was further reduced to 2.5 cm, and the enhanced portion of the tumor lesion disappeared. AFP and PIVKA-II levels were 5.3 ng/mL and 36 mAU/mL, respectively. The Child-Pugh score was 5 (class A). This was considered complete response according to the modified Response Evaluation Criteria in Solid Tumors.¹¹

Figure 1. Imaging studies at initial diagnosis and follow-up visits. (A) Liver MRI at initial diagnosis. A 4.7 cm-sized mass was noted at the porta hepatis, extending up to the right 2nd ordered branch and left 1st ordered branch. The tumor showed arterial enhancement and a delayed washout pattern. (B) One month post-SBRT and after 2 cycles of HAIC, the tumor size decreased from 4.7 cm to 4 cm, and the patency of the left portal vein was almost fully restored. (C) Seven months post-SBRT and after 6 cycles of HAIC (i.e., HAIC completion), the tumor size was further decreased (to 2.5 cm) and the enhanced portion of the tumor disappeared. (D) Eleven months post-SBRT, common hepatic duct enhancement and intrahepatic duct dilatation were noted. The total bilirubin was elevated to 17.45 mg/dL. (E) Thirteen months post-SBRT, a liver abscess of 8.1 cm was noted at the left lateral lobe of the liver. (F) Fifteen months post-SBRT, severe ascites with multiple liver abscesses were observed. (G) Temporal change of AFP and CP score after SBRT. MRI, magnetic resonance imaging; SBRT, stereotactic body radiotherapy; HAIC, hepatic arterial chemotherapy; AFP, alpha-fetoprotein; CP score, Child-Pugh score.

At 11 months post-SBRT and after 6 cycles of HAIC, common hepatic duct enhancement and intrahepatic duct dilatation were noted on follow-up CT. The total bilirubin was elevated to 17.45 mg/dL, and the Child-Pugh score was 8 (class B). The AFP level was within normal range (5 ng/mL), but PIVKA-II was elevated to 277 mAU/mL. After pigtail plastic stent insertion, the total bilirubin normalized to 1.26 mg/d, and the Child-Pugh score was decreased to 6 (class A).

At 13 months post-SBRT, the patient visited the emergen-

cy department because of fever, hyperventilation, and drowsiness. A liver abscess at the left lateral lobe (8.1 cm) and mild ascites were noted on CT. Sono-guided percutaneous abscess drainage was performed and enterococcus faecalis was grown in culture. Antibiotic therapy was initiated; the patient's condition fluctuated but ultimately deteriorated further. AFP and PIVKA-II levels were 2.7 ng/mL and 48 mAU/mL, respectively. The Child-Pugh score was 7 (class B). At 15 months post-SBRT, the patient was re-admitted due to exacerbation of fe-

Figure 2. Stereotactic body radiotherapy planning to treat the tumor at the porta hepatis. (A) Schematic delineation of radiation dose distribution. (B) Dose-volume histogram showing the doses received by organs and the relevant volumes.

ver and of the abscess on imaging. AFP and PIVKA-II levels at this point were 2.8 ng/mL and 62 mAU/mL, respectively; the Child-Pugh score was 11 (class C), and severe ascites with multiple liver abscesses were observed on CT. The patient died 5 days after admission owing to uncontrolled fever, leukocytosis, and progression to sepsis. The liver images obtained over time are shown in Fig. 1.

DISCUSSION

Portal vein invasion is found in 10–40% of HCC patients at diagnosis¹²; curative treatment is challenging, and such patients only survive 2–4 months with best supportive care.^{12,13} EBRT has been commonly applied to HCC with portal vein invasion with its availability to treat encompassing major vessels.² Median survival times in previous studies ranged from 7 to 12 months, and the response rate was 35–62%.¹³ Unlike the past, TACE is safely performed for the cases of HCC with portal invasion, and the survival benefit was shown in recent

prospective studies.^{14,15} HAIC is less commonly administered than TACE, but has the advantage of delivering high doses of chemotherapeutic drugs to tumors directly via tumor-feeding arteries without developing post-embolization complications. In clinical practice, chemotherapeutic local treatment including TACE and HAIC are used in combination with EBRT to maximize the therapeutic efficacy.^{5,6}

EBRT with conventional fractions, usually performed for 5–7 weeks using 1.8–2.5 Gy per fraction, is a good palliation method conferring a modest extension of survival, but is not regarded as curative even when combined with local chemotherapeutic modalities. On the other hand, SBRT can be performed with curative intent. Prospective studies have shown local control rates of about 90%.^{16,17} A recent meta-analysis showed that SBRT had better response rate than conventional EBRT in treatment of HCC with PVT (70.7% [95%CI 63.7–76.8] vs. 51.3% [95% CI: 45.7–57.0]).¹⁸ In the same meta-analysis, most common grade ≥ 3 side effects of conventional EBRT were lymphocytopenia, gastric/duodenal ulcer, and liver function deterioration. Grade ≥ 3 biliary toxicities were reported in 3 of 21 studies. Although SBRT was associated with fewer side effects than conventional EBRT in general, but two of three studies reported grade ≥ 3 biliary toxicities.

Two studies attributed biliary toxicity caused by SBRT to its effect on the central hepatobiliary tract. Osmundson et al.¹⁹ reported that 24% of grade ≥ 2 and 18% of grade ≥ 3 biliary toxicities, and suggested $V_{BED10/72} < 21 \text{ cm}^3$ (5-fractionated SBRT: $V_{40} < 21 \text{ cm}^3$; 3-fractionated SBRT: $V_{33.8} < 21 \text{ cm}^3$), $V_{BED10/66} < 24 \text{ cm}^3$ (5-fractionated SBRT: $V_{37.7} < 24 \text{ cm}^3$; 3-fractionated SBRT: $V_{32} < 24 \text{ cm}^3$) as constraints to reduce biliary toxicity. Eriguchi et al.²⁰ performed SBRT with 35–50 Gy in 5 fractions and reported radiation-induced biliary stenosis in only 1 of 50 patients; they concluded that 40 Gy SBRT to the central biliary system in 5 fractions is safe.

Our patient maintained complete response until his last follow-up visit. The patient experienced a grade 3 biliary stricture during follow-up and died of liver abscess-related complications. The cause of this abscess was unknown and may have been multifactorial; various treatments and procedures such as chemoport insertion, SBRT, HAIC, and stent insertion might have contributed to the complications. To date, no studies

have been conducted exclusively on SBRT and HAIC combined treatment for HCC that involves the portal vein, or the related side effects. Our case suggests that combining SBRT and HAIC may have potent therapeutic efficacy, and that careful consideration should be given to possible complications including biliary toxicity.

AUTHOR CONTRIBUTIONS

Chai Hong Rim mainly wrote the manuscript. Won Sup Yoon designed the study. All the authors supervised the manuscript and approved the final version for publication.

Conflicts of Interest

The authors have no conflicts of interests to disclose.

REFERENCES

- European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56:908-943.
- Rim CH, Seong J. Application of radiotherapy for hepatocellular carcinoma in current clinical practice guidelines. *Radiat Oncol J* 2016;34:160-167.
- Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-390.
- Park HC, Yu JJ, Cheng JC, Zeng ZC, Hong JH, Wang ML, et al. Consensus for Radiotherapy in Hepatocellular Carcinoma from The 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014): Current Practice and Future Clinical Trials. *Liver Cancer* 2016;5:162-174.
- Yoon SM, Lim YS, Won HJ, Kim JH, Kim KM, Lee HC, et al. Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. *Int J Radiat Oncol Biol Phys* 2012;82:2004-2011.
- Lee HS, Choi GH, Choi JS, Kim KS, Han KH, Seong J, et al. Surgical resection after down-staging of locally advanced hepatocellular carcinoma by localized concurrent chemoradiotherapy. *Ann Surg Oncol* 2014;21:3646-3653.
- Sanuki N, Takeda A, Kunieda E. Role of stereotactic body radiation therapy for hepatocellular carcinoma. *World J Gastroenterol* 2014;20:3100-3111.
- Matsuo Y, Yoshida K, Nishimura H, Ejima Y, Miyawaki D, Uezono H, et al. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: evaluation by comparison with conventional three-dimensional conformal radiotherapy. *J Radiat Res* 2016;57:512-523.
- Xi M, Zhang L, Zhao L, Li QQ, Guo SP, Feng ZZ, et al. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. *PLoS One* 2013;8:e63864.
- Lee JM, Park JW, Choi BI. 2014 KLCSSG-NCC Korea Practice Guidelines for the management of hepatocellular carcinoma: HCC diagnostic algorithm. *Dig Dis* 2014;32:764-777.
- Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60.
- Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol* 2006;12:7561-7567.
- Chan SL, Chong CC, Chan AW, Poon DM, Chok KS. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. *World J Gastroenterol* 2016;22:7289-7300.
- Luo J, Guo RP, Lai EC, Zhang YJ, Lau WY, Chen MS, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. *Ann Surg Oncol* 2011;18:413-420.
- Niu ZJ, Ma YL, Kang P, Ou SQ, Meng ZB, Li ZK, et al. Transarterial chemoembolization compared with conservative treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: using a new classification. *Med Oncol* 2012;29:2992-2997.
- Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RK, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 2013;31:1631-1639.
- Kang JK, Kim MS, Cho CK, Yang KM, Yoo HJ, Kim JH, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer* 2012;118:5424-5431.
- Rim CH, Kim CY, Yang DS, Yoon WS. Comparison of radiation therapy modalities for hepatocellular carcinoma with portal vein thrombosis: a meta-analysis and systematic review. *Radiation Oncol* 2017 Dec 9. pii: S0167-8140(17)32730-5. doi: 10.1016/j.radonc.2017.11.013. [Epub ahead of print]
- Osmundson EC, Wu Y, Luxton G, Bazan JG, Koong AC, Chang DT. Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. *Int J Radiat Oncol Biol Phys* 2015;91:986-994.
- Eriguchi T, Takeda A, Sanuki N, Oku Y, Aoki Y, Shigematsu N, et al. Acceptable toxicity after stereotactic body radiation therapy for liver tumors adjacent to the central biliary system. *Int J Radiat Oncol Biol Phys* 2013;85:1006-1011.