Curative effect of stereotactic body radiotherapy on hepatic hilar carcinoma

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Abstract. This study was conducted to investigate the effect of stereotactic body radiotherapy (SBRT) on hepatic hilar tumors. Between October, 2006 and October, 2012, we analyzed 63 unresectable hepatic hilar tumors that were treated by SBRT at the Department of Radiation Oncology, 323 Hospital of the People's Liberation Army, Xi'an, China. The patients received a total radiation dose of 45 Gy (range, 44-48 Gy) with a dose fractionation of 3-6 Gy/fx, administered for a total of 9-12 times, 2-5 times/week. At 1 and 3 months we evaluated therapeutic efficacy and 1- and 2-year survival rate. At 1 month, the patients exhibiting complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were 15 (23.8%), 34 (54.0%), 11 (17.5%) and 3 (4.7%), respectively. At 3 months, the number of cases with CR, PR, SD and PD was 22 (34.9%), 32 (50.8%), 3 (4.8%) and 6 (9.5%), respectively. The total effective rate, defined as CR + PR, was 85.7% (54/63). The number of patients with a tumor diameter of ≤5 cm in the CR, PR, SD and PD groups was 13 (72.2%), 4 (22.2%), 1 (5.6%) and 0 (0.0%), respectively. The number of patients with a tumor diameter of >5 cm in the CR, PR, SD and PD groups was 9 (20.0%), 28 (62.2%), 6 (13.3%) and 2 (4.5%), respectively. The 1-year survival rate of patients with a tumor diameter >5 cm was 71.4% (45/63) and the 2-year survival rate was 42.9% (27/63). In conclusion, SBRT appears to be a safe and effective treatment for hepatic hilar tumors.

Introduction

Clinically, tumors involving segments 1, 4, 5 and 8 of the liver are referred to as hepatic hilar tumors. This location is adjacent to and may invade major blood vessels (inferior vena cava, primary hepatic veins and portal vein) and the common bile duct. Hepatic hilar tumors may be associated with compression or invasion of blood vessels and bile ducts, causing blood flow or biliary obstruction and presenting as an acute condition. The anatomical structures located in this region are complex, making surgical resection difficult and hazardous and controlling intraoperative bleeding to improve the outcome of hepatic hilar tumor resection is a challenge to the liver surgeon. However, radiation therapy for hepatic hilar tumor is an established palliative modality, although the optimal role of radiation therapy in the treatment of liver tumours has not been well defined (1). Historically, the liver was considered to be a relatively radiosensitive organ and it may be difficult to achieve the radiation doses required to eradicate gross tumours without causing radiation-induced liver disease (RILD), which develops ~4-8 weeks following radiation therapy (2). RILD symptoms include ascites, rapid weight gain, increased abdominal girth and increased levels of alkaline phosphatase. To limit RILD, studies have shown that the whole-liver irradiation dose must remain <30-35 Gy, with a conventional 2 Gy per fraction (3-5). In this study, we investigated whether stereotactic body radiotherapy (SBRT) is an effective and safe curative method for the treatment of unresectable hepatic hilar tumors.

Material and methods

Clinical data. Between October, 2006 and October, 2012, we randomly selected 63 patients with hepatic tumors from the Cancer Center of the 323 Hospital of the People's Liberation Army (PLA), Xi'an, Shaanxi, China to undergo SBRT. The tumors included primary hepatocellular carcinoma (HCC) in 16 cases, cholangiocarcinoma in 27 cases, liver metastatic carcinoma in 16 cases and hepatic angiosarcoma in 4 cases. The patients included 40 men and 23 women, with a mean age of 55.2 years (range, 46-82 years). The hepatic tumors were classified as stage I, II, III and IV and the Child-Pugh class was graded as A, B and C. There were 5 grades according to the Karnofsky performance status, namely 90, 80, 70, 60 and 50 points. All the hepatic cancer patients were diagnosed by enhanced computed tomography or magnetic resonance imaging and were divided into 2 groups according to tumor size, namely patients with tumors sized ≤5 cm and those with tumors sized >5 cm. The patient characteristics are summarized in Table I. This study was approved by the

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Ethics Committee of the 323 Hospital of PLA and the patients provided written informed consent prior to their enrolment.

Treatment planning. We performed radiotherapy using the 'super gamma-knife' SGS-I Stereotactic Gamma-Ray system (Huiheng Medical Inc., Shenzhen, China), which focused on whole-body radiation, and the UNICORN 3D Treatment Planning System (Huiheng Medical Inc.) for the design. Outlining of the target area-gross tumor volume (GTV) was performed by a medical physicist and the planning target volume (PTV) was extended 0.5 cm outside the GTV. The organs at risk included the normal liver, duodenal pancreas, kidney and spinal cord. We ensured the isodose curve covered the 50% of PTV and that the radiation delivered to normal tissue did not exceed the tolerance dose. A dose-volume histogram (DVH) was drawn to evaluate the square and optimize the radiation scheme. The radiation treatment prescription dose was as follows: 3-6 Gy/fx, for a total of 9-12 times, 2-5 times/week, up to a total dose of 44-48 Gy. We tried to steer clear of important tissues and determine the treatment plan optimization index with DVH: Thre were 50 to 90% DVH surrounded the PTV; The dose given in adjacent target organs were not exceeded 25 Gy, which was tolerance dose. During treatment, the patients were administered drugs such as static drops of liquorice anhydride, while avoiding to use any chemicals. The treatment dose fractions are listed in Table II.

Clinical observation. We established the observation indices of the curative effect as follows: Decrease in bilirubin levels at 1 and 3 months; changes in the size of the tumor and portal vein tumor emboli with treatment; 1- and 2-year survival rate; percentage of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD); overall survival (OS) for all the patients who underwent treatment with the 'super gamma-knife' system. Using these indices, we performed a comprehensive evaluation of the curative effect of SBRT.

Efficacy evaluation. Efficacy evaluation was performed according to the World Health Organization curative effect evaluation standards of solid tumors (6).

Statistical analysis. The SPSS software, version 19 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses for OS.

Results

Curative effect. At 1 month, the patients exhibiting CR, PR, SD and PD were 15 (23.8%), 34 (54.0%), 11 (17.5%) and 3 (4.7%), respectively. At 3 months, the number of patients with CR, PR, SD and PD was 22 (34.9%), 32 (50.8%), 3 (4.8%) and 6 (9.5%), respectively. The total effective rate (CR + PR) was 85.7% (54/63). The number of patients with a tumor diameter ≤ <5 cm in the CR, PR, SD and PD groups was 13 (72.2%), 4 (22.2%), 1 (5.6%) and 0 (0.0%), respectively. The number of patients with a tumor diameter of >5 cm in the CR, PR, SD and PD groups was 9 (20.0%), 28 (62.2%), 6 (13.3%) and 2 (4.5%), respectively. The curative effect is presented in Table III.

Table I. Patient characteristics.

Characteristics	No. of patients
Gender	
Male	40
Female	23
Type of tumor	
Primary hepatocellular carcinoma	16
Cholangiocarcinoma	27
Liver metastatic carcinoma	16
Hepatic angiosarcoma	4
Stage	
I	20
II	6
III	32
IV	5
Child-Pugh class	
A	25
B	23
C	15
Diameter of tumor, cm	
>5	45
≤5	18
Karnofsky performance status, points	
90	20
80	13
70	12
60	15
50	3

Adverse reactions and complications. The patients presented with different degrees of gastrointestinal tract reactions during treatment, such as nausea, mild vomiting and poor appetite. There was no reported digestive tract hemorrhage or severe vomiting. Following symptomatic treatment, the patients' symptoms subsided.

Survival following treatment. The patients were followed up for 6-28 months, with a median follow-up of 12 months. The 1-year survival rate of patients with a tumor diameter of >5 cm was 71.4% (45/63) and the 2-year survival rate was 42.9% (27/63). The median survival time was 24 months. A total of 36 patients succumbed to the disease, of whom 12 died from upper gastrointestinal bleeding. The OS graph is presented in Fig. 1.

Discussion

Hepatic hilar carcinoma is adjacent to the main intrahepatic blood vessels and its surgical resection is difficult. Liver surgery for hepatic hilar carcinoma is associated with severe complications and a poor curative effect (7). Radiofrequency ablation technology is an alternative to surgery for liver cancer treatment; however, bile flow velocity is low in the bile duct and heat is slowly dissipated. Therefore, during radiofrequency ablation,

Table II. Treatment dose fractions.

Characteristics	Total dose irradiation (Gy)	Gy/fx	Times
Primary hepatocellular carcinoma	45	5	9
Cholangiocarcinoma	44	4	11
Liver metastatic carcinoma	48	4	12
Hepatic angiosarcoma	45	5	9

Table III. Curative effect.

	At 1 month		At 3 months		≤5 cm (n=18)		>5 cm (n=45)	
Type of response	No.	%	No.	%	No.	%	No.	%
CR	15	23.8	22	34.9	13	72.2	9	20.0
PR	34	54.0	32	50.8	4	22.2	28	62.2
SD	11	17.5	3	4.8	1	5.6	6	13.3
PD	3	4.7	6	9.5	0	0.0	2	4.5

CR, complete response; PR, partial response; SD, stable disease; and PD, progressive disease.

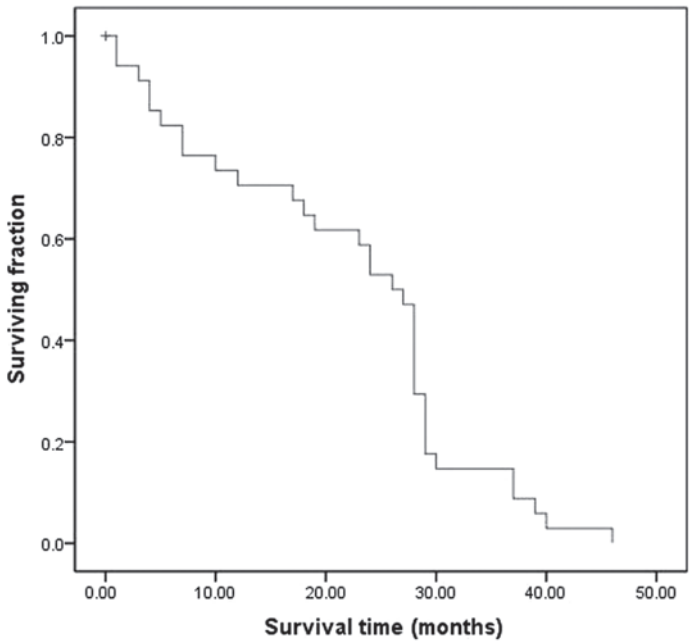

Figure 1. Overall survival for all patients treated with stereotactic body radiotherapy.

there is a risk of damaging the common bile duct, causing bile leakage or bile duct strictures. Hepatic hilar tumors were considered a contraindication for heat coagulation treatment (8,9). However, the radiofrequency ablation techniques have improved significantly and, combined with hepatic artery embolization, have achieved good results; however, this treatment was considered suitable for lesions <7 cm and required earlier-stage patients (10,11). As this treatment exerts a significant effect on the patient's overall condition and liver function, it is only suitable for most patients with malignant liver tumor. In cases with obstructive jaundice caused by bile duct compression, surgery may not be feasible and the degree of difficulty of minimally invasive treatment is significantly increased. The majority of the patients require bile duct drainage, stent placement and other minimally invasive approaches, which require a long time, are costly and exhibit poor effectiveness.

SBRT is the application of 3-dimensional (3D) positioning technology and special radiation equipment, which appears to be more effective. SBRT focuses 3D space high-energy rays on a certain target in the body to ensure the tumor receives high-dose

irradiation, minimizing the irradiation of the surrounding normal tissues. When using X-ray or gamma-rays in SBRT, it may be referred to as X-knife or gamma-knife. The application of SBRT technology in the treatment of liver cancer has gradually been proven to be a safe and effective option (12-16). Kim *et al* (17) conducted a study on 70 HCC patients who were unsuitable for conventional resection or transcatheter arterial chemoembolization and received 3D-conformal radiation therapy treatment. The results demonstrated an effective rate of 54.3% and a median survival time of 18 months. Dang *et al* (18) reported a curative effect with the 'gamma-knife' in 56 patients with primary liver cancer, with an effective rate of 71.5% and a median survival time of 10.6 months; of note, the effective rate for tumor diameter <5 cm was 90%. SBRT for liver metastases over the last few years has exhibited satisfactory curative effects (19-21). SBRT also plays a role in locoregional control, is not associated with pain and has fewer complications; therefore, it may be considered as an effective method for comprehensive treatment of liver tumors (1).

Body gamma-knife is one of the SBRT applications, which has the characteristics of conformal therapy with a single high dose and a short treatment time. Thus, it significantly improves the curative effect and reduces the reaction to the radiation and the degree of damage.

In conclusion, our data were based on liver tumors and gamma-knife technical characteristics. The patients included in our study had primary liver cancer, liver metastases and hepatic angiosarcoma. The effective rate at 1 month and at 3 months after treatment was 77.8 and 85.7%, respectively. A total of 6 patients succumbed to the disease within 3 months, of whom 5 patients had stage IV and 1 had stage III disease, all exhibiting poor general condition and accompanied by portal vein tumor emboli. Of those 6 patients, 2 succumbed to upper gastrointestinal bleeding, 3 to cancer cachexia and 1 to hepatic failure. The tumor volume of four hepatic angiosarcoma patients became smaller. The 1-year survival rate of patients with a tumor diameter >5 cm was 71.4% (45/63) whereas the 2-year survival rate was the same. The treatment efectiveness was higher for tumors with a diameter of <5 cm was higher compared to that previously reported as the curative effect of gamma-knife therapy for liver cancer (18). As our cases exhibited a higher percentage of cholangiocarcinoma and liver metastases, SBRT exerted a good curative effect for these two diseases (22). In addition, the direct bilirubin of patients decreased and in 75% (36/48) of the patients the levels returned to normal. At 3 months, the total and direct bilirubin levels in 83.3% (40/48) of the cases had returned to normal and was close to normal in the remaining cases, with almost all patients achieving a complete symptom relief. Therefore, SBRT is a viable option for the treatment of for hepatic tumors, particularly in cases with late-stage disease, poor general condition and unsuitable for resection or minimally invasive surgery. However, treatment refinement to improve the curative effect and the long-term survival rate of patients with hepatic tumors requires further investigation.

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