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Research Article

Observation of Stereotactic Radiosurgery (Cyberknife) on Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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Abstract: The purpose of the study was to analyze the clinical effect of stereotactic radiosurgery (SRS) (Cyberknife) on hepatocellular carcinoma with portal vein tumor thrombosis (HCC-PVTT). Data from 50 patients with HCC-PVTT who received Cyberknife from August 2013 to April 2016 was collected for efficacy analysis. Moreover, survival correlation was evaluated by Cox proportional-hazards model. The total effective rate in 1–3 months after treatment was 64.00%, including 7 cases in complete remission, 12 cases in partial remission, 13 cases in stable conditions, and 18 cases with enlargement; a 4–24-months follow-up (with an average of 11.58 ± 2.58 months) showed that median survival, 1-year cumulative survival rate, and 2-year cumulative survival rate were, respectively, 11.86 ± 1.79 months, 48.00%, and 20.00%. Moreover, the Cox proportional-hazards model indicates that it was with no correlation between lesion diameter, classification of liver function, pre-operative alpha-fetoprotein, types of hepatitis, number of tumors, ascites, types of tumor emboli, total dose, and survival rate. SRS is effective for HCC-PVTT and serves as an ideal treatment clinically to help preserve patients' lives, which is worthy of clinical promotion and application.

Keywords: *hepatocellular carcinoma; portal vein tumor thrombosis; stereotactic radiosurgery; efficacy*

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0 Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary malignancy in China. Patients with HCC suffer from liver pain, systemic and digestive system symptom, and hepatomegaly, etc. It has not been fully elucidated of the pathogeny and pathogenesis of HCC which, however, is recognized to be associated with chemical carcinogens such as cirrhosis, viral hepatitis, and aflatoxin. As a common complication of HCC, portal vein tumor thrombosis (PVTT) is induced by portal venous counterflow with portal hypertension as the internal cause and arterial-portal venous shunts as the external cause. Combination of HCC and PVTT increases the complication of clinical treatment and make it impossible for operation. Hepatic arterial chemoembolization is the main treatment for HCC-PVTT. Nevertheless, it is not applicable for patients without effective collateral circulation due to portal vein obstruction[1]. In recent years, it is found that precise external-beam radiotherapy should be applied more in the treatment of HCC-PVTT. Moreover, stereotactic radiosurgery (SRS) appears accordingly and gains more attention from scholars and clinicians. This paper collected data from 50 patients with HCC-PVTT from August 2013 to April 2016 and analyzed SRS (Cyberknife) on HCC-PVTT for clinical reference.

1 Data and methods

1.1 General data

Data were collected from 50 patients with HCC-PVTT admitted to our hospital from August 2013 to April 2016

1.1.1 Inclusion criteria

1. All patients were diagnosed by B-mode ultrasound of liver, computed tomography (CT) scan, and alpha-fetoprotein (AFP) blood test and the results of which were in line with the clinical criteria of HCC.
2. All patients showed good physical strength with a life expectancy >3 months and Karnofsky score >60.
3. All patients conformed to the indication of SRS.
4. This study was approved by the Ethics Review Board of the hospital and was known by patients and their family members, who voluntarily signed the consent letters.

1.1.2 Exclusion criteria

The following criteria were excluded from the study:

1. Pregnant and lactating patients.
2. Patients with other cancers
3. Patients with other visceral dysfunction.
4. Life expectancy <3 months.
5. Patients during acute or chronic infection. There were 24 male patients and 26 female patients aging from 40 to 75 with an average age of 61.05 ± 3.18 in this study.

Their tumor size was 2.15~7.52 cm with an average of 5.15 ± 1.74 cm, and pre-operative AFP was 10.58~27.56 μg/m with an average of 20.89 ± 2.74 μg/ml. Moreover, there were 42 cases with a single tumor and the other 18 cases with multiple tumors; 13 cases with ascites and the other 47 cases without ascites; 55 cases with hepatitis B and the other 5 cases with hepatitis C.

1.2 Methods

All patients were diagnosed by relevant tests after being admitted, including routine blood test, physical examination, coagulation test, heart, kidneys, liver, and lung function test, and B-mode ultrasound. Excluding radiation therapy contraindications, all patients were treated with CT-guided placement of gold fiducial markers. Lidocaine was applied for intraoperative local anesthesia, and the puncture was completed in a sterile environment. A 6–12 h post-operative staying-in-bed was instructed with necessary hemostatic intervention, and the vital signs of patients were closed monitored. Around 5–7 days after the operation, vacuum pads were fixed (according to the position required by radiation therapy) and positioned by multi-slice helical CT for scanning images which would be input into the treatment plan system for target delineation. Various imaging technologies were adopted, including magnetic resonance imaging (MRI) and PER-CT to outline the gross tumor volume. Since tumor thrombus is similar with the primary tumor, they could be outlined at the same time.

Taking palliative treatment as the principle, tumors whose lesion diameters were <5.0 cm were expanded by 1.5–2.0 cm; tumors whose lesion diameters were within 5–10 cm were expanded by 0.5–1.5 cm; and tumors whose lesion diameters were >10.0 cm were expanded by 0.1–0.5 cm. 100% line was selected as the coverage of the target and determined as the prescribed dose. Implement as planned once the plan was confirmed. G4 Cyberknife SRS system (Accuracy Inc.) was adopted for radiation therapy. Golden standard tracking and respiratory tracking were applied to prevent surrounding organs being damaged and ensure the dose should not exceed the tolerance dose in patients. Delineated volumes were 24.5~1264.9 cm^3 with an average of 399.58 ± 15.84cm^3; dose separation was once 5~13Gy; irradiation times vary from 4 to 8; and tumor dose was 34~55Gy. Irradiate every day or every 1–2 days based on patients' conditions. All patients were treated with corresponding liver protective drugs before and after treatment. Moreover, blood routine test, as well as liver and kidney functions, was closely observed to avoid severe adverse effects.

1.3 Observation index

To analyze the correlation between lesion diameter, classification of liver function, pre-operative AFP, types of hepatitis, number of tumors, ascites, types of tumor emboli, total dose, and survival rate.

1.4 Efficacy index

After 1–3 months of treatment, liver re-examination was completed by CT and MRI. Moreover, efficacy was evaluated by solid tumor (RECIST1.1):[2] (1) Incomplete remission: Clinical symptoms and signs were significantly improved; liver lesions and PVTT both disappeared and the tumor markers returned to normal. (2) In partial remission: Clinical symptoms and signs were relieved; lesions within the liver were reduced by over 25%; further imaging examination showed that the activity of PVTT was significantly reduced. (3) In stable conditions: Clinical symptoms and signs were

improved to some extent; lesions within the liver were reduced by <25% or increased by <20%; there was no obvious reduction or progress in PVTT. (4) Failed the above criteria or patients suffered from deterioration and even died. Total effective rate = complete remission rate + partial remission rate + stable conditions rate.

1.5 Statistical method

Input data during the study to SPSS21.0 for processing with $P < 0.05$ as statistically significant. Independent Sample *t*-test was adopted for measurement data "mean ± standard deviation" and Chi-square test was applied to count data "ratio." Survival time was analyzed by lifecycle methods. Survival curve drawn was analyzed by Cox proportional-hazards model to evaluate the factors affecting patients' survival time.

2 Results

2.1 Efficacy

The total effective rate in 1–3 months after treatment is 64.00%, including 7 cases in complete remission, 12 cases in partial remission, 13 cases in stable conditions, and 18 cases with enlargement [Table 1]; a 4–24-months follow-up (with an average of 11.58 ± 2.58 months) shows that median survival, 1-year cumulative survival rate, and 2-year cumulative survival rate are, respectively, 11.86 ± 1.79 months, 48.00%, and 20.00%.

Table 1. Efficacy (*n*, %)

Efficacy	Case(s) (%)
Incomplete remission	7 (14.00)
In partial remission	12 (24.00)
In stable conditions	13 (26.00)
With enlargement	18 (36.00)
Total effective rate	32 (64.00)

2.2 Cox proportional-hazards model

The Cox proportional-hazards model indicates that it was with no correlation between lesion diameter, classification of liver function, pre-operative AFP, types of Hepatitis, number of tumors, ascites, types of tumor emboli, total dose, and survival rate [Table 2].

3 Discussion

During the progressive phase of HCC, PVTT is its most common and most severe complication which is with a higher incidence rate, disability rate, and fatality rate. PVTT can easily lead to the dissemination of hepatic embolic tumor and portal hypertension in patients with HCC. Previous analysis indicated that the survival rate of patients would be lower than 3 months without prompt treatment. In addition, HCC-PVTT, whose treatment mainly focuses on non-operation options, cannot be treated by operation[3]. Hepatic arterial chemoembolization has been adopted in previous treatment, which could control primary lesion, but shows obvious limitations, i.e., could not gain efficacy for PVTT as expected. In addition, hepatic arterial chemoembolization is a taboo for patients suffering from portal vein thrombus but without collateral circulation. Therefore, it is obviously limited while being applied.

As a hot topic at home and abroad, precise radiotherapy plays an important role in the diagnosis of tumors which cannot be treated by operations. Tao[4] indicated that the 1-year survival rate stayed around 34.00%, and the average life expectancy reaches about 9 months for

Table 2. Cox proportional-hazards model analysis

Index	b	Wald χ^2	*P*	RR	RR 95% CI	
					Upper limit	Lower limit
Lesion diameter	−0.431	0.826	0.369	0.648	1.651	0.254
Classification of liver function	−0.489	1.638	0.215	0.617	1.289	0.289
Pre-operative AFP	−0.069	0.035	0.849	0.933	1.910	0.458
Types of hepatitis	−0.905	1.945	0.159	0.401	1.445	0.114
Number of tumors	−0.402	1.300	0.252	0.668	1.335	0.333
Ascites	0.662	2.748	0.097	1.943	4.250	0.886
Types of tumor emboli	−0.412	0.468	0.658	0.679	2.365	0.189
Total dose	0.335	1.012	0.313	1.389	2.387	0.729
CI: Confidence interval, AFP: Alpha-fetoprotein						

patients after radiotherapy, which are both prolonged compared with patients who did not treated by radiotherapy (survival rate was around 11.00% and the median of life expectancy stayed at 4 months). Ruisha *et al*.[5] reported that the life expectancy was around 8 months of patients with HCC-PVTT who received three-dimensional conformal radiation therapy. At present, studies on the combination of radiotherapy and hepatic arterial chemoembolization to improve the efficacy in the treatment of HCC-PVTT have been carried out and showed that such combination differed little from operations. Further clinical studies have been carried out, and the treatment guidelines for HCC-PVTT indicated that radiotherapy should be applied in time for patients with PVTT who could not receive completed resection of lesion or thrombus.

As an image-guided radiation therapy, Cyberknife was reported to effectively protect liver tissue around the lesion and improve the tolerance dose of a blood vessel for radiation, which was also the theoretical basis of SRS on HCC-PVTT. Cyberknife minimized patients' hospitalization and treatment time with larger divided dose and less radiation times, which was more acceptable for clinicians and patients and worthy for clinical promotion[6]. In this study, the total effective rate, median survival, 1-year cumulative survival rate, and 2-year cumulative survival rate were, respectively, 64.00%, 11.86 ± 1.79 months, 48.00%, and 20.00%, which was in line with the results of previous studies[7]. It showed that SRS bore reasonable therapeutic benefit. In addition, Cox proportional-hazards model presented that it was with no correlation between lesion diameter, classification of liver function, pre-operative AFP, types of hepatitis, number of tumors, ascites, and types of tumor emboli, total dose, and survival rate. The results may rely on the fact that most patients in this study were in the advanced phase with limit life expectancy and the cases were not limited[8]. Therefore, the conclusion should be further confirmed.

In summary, SRS is effective for HCC-PVTT and serves as an ideal treatment clinically to help preserve patients' lives, which is worthy of clinical promotion and application.

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