Original Article

Clinical Outcomes of Stereotactic Body Radiation Therapy in Patients with Liver Tumor: A Single Institution Study

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Background: Hepatic cancer is a global major health threat with a relatively high mortality rate. Standard treatment of the disease includes resection and liver transplantation.

Objective: To determine clinical outcomes of stereotactic body radiation therapy in patients with liver tumor.

Materials and Methods: Patients with primary hepatic tumors or cholangiocarcinoma of stage I to IIIB in TNM staging and those with liver metastases were included in the study for analyses of tumor response rate, local tumor control, disease-free survival, and overall survival after stereotactic body radiation therapy [SBRT].

Results: Among 25 tumor masses in 19 patients analyzed, the overall tumor response rate was 56% (complete response 32%; partial response 24%). The median administered biologically effective dose in Gy_{10} was 100 Gy. Local tumor control rates were 87.5% and 65.6% for two and three years, respectively. Disease-free survival was 41.2% and 15.4% for two and three years, respectively. The overall survival of the patients was 70.75% at one year. Tumors larger than 19.46 cc or 3.3 cm in diameter were associated with inferior tumor response rate.

Conclusion: These results suggest that SBRT might be an effective therapy in hepatic tumors given its high local tumor control rate. The major limitation of the treatment modality remains hepatic function of the patients, which restricts doses to the tumor.

Keywords: Stereotactic body radiation therapy, Liver tumor, Hepatoma, Clinical outcomes

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Liver cancer is the fifth most common cancer and one of the most fatal cancers, causing approximately 750,000 deaths worldwide annually[1]. Hepatocellular carcinoma [HCC], a primary liver cancer, accounts for most liver cancers. Risks factors of HCC include hepatitis B or C virus infection, cirrhosis, and autoimmune disease of liver. Chronic liver injury sharply increases the cancer risk[2]. Management of HCC consists of resection, liver transplantation, and radiofrequency ablation for curative treatments. Transarterial chemoembolization and sorafenib are the standard treatments for palliative care of HCC following the Barcelona Clinic Liver Cancer [BCLC] staging system[3]. Radiation therapy is typically not an option for treatment of HCC because of limited liver function of the patients as well as potential radiation-induced liver disease [RILD], which may occur within a few months after hepatic irradiation[4]. However, there has been renewed interest due to advances in the

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stereotactic radiation therapy technique, particularly for unresectable hepatic cancer. Stereotactic body radiation therapy [SBRT] delivers high doses of radiation to the target tumor with only a few irradiation fractions. By using highly precise treatment fields the technique can limit radiation dose to normal tissue surrounding the tumor while delivering an ablative treatment to the tumor. The high local control rate and acceptable morbidity make SBRT a feasible method for the treatment of liver tumor[5-7]. A local tumor control rate of greater than 90% for up to three years can be achieved with SBRT. These reports have also emphasized that although liver SBRT can be a therapy of choice, management of patients with Child-Pugh [CP] class B needs careful consideration as liver toxicity could potentially arise[8-10]. The major limiting parameter for HCC SBRT remains hepatic function, for which Child-Pugh progression is the dose-limiting factor, thus patients with CP class A typically have longer survival rates than patients with CP class B[11]. Our current study aimed to describe and report clinical results of SBRT for liver cancer at Chulabhorn Hospital based on our experience in management of the disease.

Materials and Methods

We retrospectively reviewed medical and follow-up records of patients with primary liver cancer or liver metastases who received SBRT at Chulabhorn Hospital (Bangkok, Thailand) between March 2012 and July 2016. The patients were followed-up until February 2017.

For hepatocellular carcinoma, we included patients with HCC who could not undergo surgery, transarterial chemoembolization, or other local ablative procedure. For liver metastasis, we included patients who had unresectable liver metastasis and limited extrahepatic disease. For intrahepatic cholangiocarcinoma, we included patients who had unresectable disease with no extrahepatic metastasis.

A tumor board that included a hepatobiliary surgeon, a medical oncologist, a radiation oncologist, a nuclear medicine radiologist, and a diagnostic radiologist evaluated all patients before making the decision to administer SBRT.

The patients were immobilized with Pro-Lok system (CIVCO medical solution) and had abdominal compression to reduce liver motion. After the immobilization process, CT simulation with a slice thickness of 3 mm was initiated 45 seconds after intravenous injection of contrast media. A 4D-CT scan was performed in all patients.

Target delineation was defined in accordance with the International Commission on Radiation Units and Measurements Report 50 [ICRU 50]. The gross tumor volume [GTV] was a liver tumor mass. The internal target volume [ITV] was GTV contoured in all phases of 4D-CT scan. The clinical target volume [CTV] included 0 to 10 mm expansion around the GTV. The planning target volume [PTV] included 5 to 10 mm expansion around the CTV.

Over the study period, we used several dose fractionation schemes in our department. To compare the prescription dose between patients, a biological equivalent dose in Gy_{10} [BED Gy_{10}] was used for analysis. Daily cone beam CT scan was used as image-guided radiation therapy technology to verify the position of the tumor before each treatment.

The patients were followed-up at one and three months after SBRT and then every three months. Clinical assessment was evaluated at each visit. Response to radiation was evaluated by computed tomography [CT] or magnetic resonance imaging [MRI] scans of the upper abdomen approximately three months after the treatment. The response was evaluated using RECIST criteria version 1.1.

The study was approved by the Ethics Committee Involving Human Subjects, Chulabhorn Research Institute (Reference No. 22/2557).

Statistical analysis

The primary objective of this paper was to report the tumor response rate. We also evaluated factors that might affect tumor response, including tumor volume, equivalent sphere diameter of a tumor, prescription dose in BED Gy_{10}, conformity index of the treatment planning, gradient measure index of the treatment planning, and treatment time of each irradiation. In subgroup of hepatocellular carcinoma patients, we evaluated whether the GTV included tumor thrombosis in major vein as an additional factor.

The secondary objective was to report local control, disease-free survival, and overall survival of the patients.

Local control [LC] was defined as time from the date of starting radiation to date of treatment failure at the site of radiation or last follow-up. Disease-free survival [DFS] was defined as time from date of starting radiation to date of failure at any site or last follow-up. Overall survival [OS] was defined as time from date of starting radiation to date of death or last follow-up.

The correlation between tumor response and candidate factors using Chi-square/Fisher's exact test.

Statistical significance was determined at *p*-value of less than 0.05. Actuarial survival time and time to other endpoints were calculated using the Kaplan-Meier method. Statistical analysis was performed using STATA SE version 12.

Results

Patient characteristics

Between March 2012 and July 2016, 19 patients with 25 liver masses were included in this study, including 15 primary liver cancers and four liver metastases. Of the 15 primary liver cancers, 14 patients had hepatocellular carcinoma and one had intrahepatic cholangiocarcinoma.

The median age of the patients was 57 years (range 43 to 75 years) and the mean age $\pm$ SD was 58.6$\pm$11 years. The patient characteristics are shown in Table 1.

The patients with hepatocellular carcinoma included three with stage I, two with stage II, two with stage IIIA, and seven with stage IIIB disease, according to the TNM staging system. Seven patients had tumor thrombus in major vein. Thirteen patients had one liver mass and one patient had four liver masses (17 liver masses in 14 patients). There was a history of chronic alcohol use in three patients, hepatitis B infection in seven patients, and hepatitis C infection in two patients.

Of four patients with liver metastasis, the primary sites of tumor were colorectal cancer in three patients and lung cancer in one patient. Pathology of all colorectal cancer patients was adenocarcinoma and pathology of the lung cancer patient was poorly differentiated squamous cell carcinoma. Two patients had one liver mass, one patient had two liver masses, and one patient had three liver masses (seven liver masses in four patients). This study included one patient with stage I intrahepatic cholangiocarcinoma according to TNM staging system.

Table 1. Patient characteristics

Patient characteristics	Number of patients	Percentage
Sex		
Male	18	94.7
Female	1	5.3
Diagnosis		
Primary liver cancer	15	78.9
Hepatocellular carcinoma	14	73.6
Cholangio carcinoma	1	5.3
Liver metastasis	4	21.1
Stage of hepatocellular carcinoma (TNM staging)		
I	3	21.4
II	2	14.3
IIIA	2	14.3
IIIB	7	50.0
Stage of intrahepatic cholangiocarcinoma		
I	1	100.0
Liver metastasis		
Primary colorectal cancer	3	75.0
Primary lung cancer	1	25.0
Number of liver tumors in patients		
1	16	84.2
2	1	5.3
3	1	5.3
4	1	5.3

Treatment outcome

The median GTV volume was 17.38 cc (range, 0.86 to 265 cc) and the median equivalent sphere diameter of GTV was 3.2 cm (range, 1.2 to 8 cm). In the HCC subgroup, the GTV included tumor thrombosis in seven patients. The median prescription dose in BED was 100 Gy_{10} (range, 45 to 150 Gy_{10}). The detailed dose fractionation schedule is shown in Table 2.

Conformity index of the treatment planning in this study ranged from 0.62 to 1.23 with a median of 1.09. Gradient measure index of the treatment planning ranged from 1.06 to 2.65 with a median of 1.49.

The treatment time of each radiation fraction was 4.1 to 16.8 minutes with a median of 7.4 minutes. The overall response rate was 56% (complete response

Table 2. Radiation dose fractionation schedule of 19 patients

Dose fractionation (BED in Gy_{10})	Number of patients
30Gy/6Fr (45)	1
36Gy/6Fr (57.6)	1
30Gy/3Fr (60)	1
39Gy/6Fr (64.35)	1
45Gy/10Fr (65.25)	2
48Gy/6Fr (86.4)	1
50Gy/5F (100)	5
54Gy/6Fr (102.6)	1
50Gy/4Fr (112.5)	1
45Gy/3Fr (112.5)	1
70Gy/10Fr (119)	1
60Gy/6Fr (120)	2
60Gy/4Fr (150)	1

[CR] 32%; partial response [PR] 24%) and 40% of patients had stable disease at the time of evaluation (approximately three months after radiation), as shown in Table 3.

The factors that significantly correlated with tumor response were GTV volume and equivalent sphere diameter of tumor. Response rate of patients with GTV volume of less than 19.46 cc was 76.92%, compared with 33.33% in patients with GTV volume >19.46 cc (p = 0.028). The response rate of patients with equivalent sphere diameter less than 3.3 cm was 76.92% compared with 33.33% in patients with equivalent diameter sphere 3.3 cm or greater (p = 0.028).

Patients who received prescription dose 100 Gy_{10} or more had a greater tumor response than patients who received prescription dose of less than 100 Gy_{10} but this difference was not statistically significant (60% vs. 50%, p = 0.62).

We did not find a statistical correlation between tumor response and conformity index or gradient measure index of treatment planning in this study. Treatment time also did not show a statistically significant correlation with tumor response.

In the subgroup of HCC patients, the group with tumor thrombosis in major vein had a lower tumor response rate than the group without this feature but the difference was not statistically significant (14.29% vs. 57.14%, p = 0.22).

Median follow-up time of the patients was 17 months. The 2-year and 3-year local control rates were 87.5% (95% CI: 38.7% to 98.1%) and 65.6% (95% CI: 15.7% to 90.9%), respectively, as shown in Figure 1.

The 2-year and 3-year DFS rate was 41.2% (95% CI: 17.4 to 63.7%) and 15.4% (95% CI: 1.2 to 45.5%), respectively. The median DFS was 6.35 months (95% CI: 2.7 to 35.3 months) as shown in Figure 2.

The 1-year overall survival rate was 70.75% (95% CI: 36.16 to 88.90), as shown in Figure 3.

Discussion

SBRT has now become established as a therapeutic option for operable and inoperable hepatic tumors[12]. A selection criterion for receiving SBRT is a relatively small tumor mass, typically no greater than 7 cm in diameter for liver tumor[13]. This selection causes less constraint to total hepatic dose, thus allowing a larger dose to be delivered to the tumor and

Table 3. Tumor response at time of evaluation of 25 tumors

Tumor response after RT	Number	Percentage
Complete response	8	32.0
Partial response	6	24.0
Stable disease	10	40.0
Progression	1	4.0

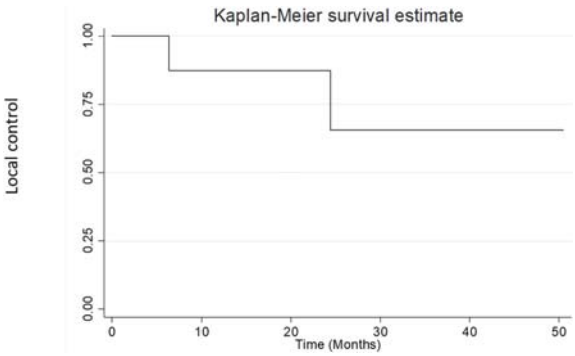

Figure 1 Kaplan-Meier plot of local control in study patients.

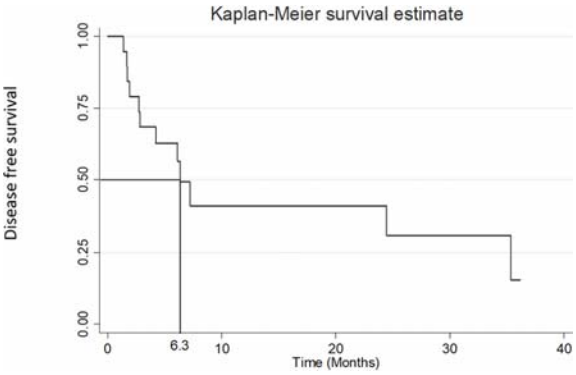

Figure 2 Kaplan-Meier plot of disease-free survival of study patients.

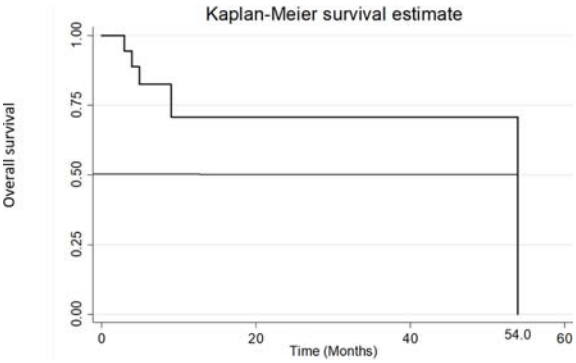

Figure 3 Kaplan–Meier plot of overall survival of study patients.

consequently a larger BED. Although our radiation delivery schemes were inconsistent, most patients received no less than 100 Gy_{10} in BED, the dose that is typically considered to yield better local tumor control[14,15]. Due to the small number of subjects, we could not find any significant difference between different BEDs. However, it is still encouraging that the response rates were better for liver masses receiving a larger BED.

The results from our institution for local tumor control were similar to those of other previous studies showing 2-year local tumor control of nearly 90%[10,16]. Factors influencing the LC were the size and volume of the tumors. As expected, larger tumors had a lower response rate. Administering a larger dose to these large tumors would be desirable; however, due to the hepatic dose constraint, particularly for patients with Child-Pugh B condition, this could prove to be difficult. Alternatively, a more advanced technique such as proton beam therapy could increase the dose to tumor while minimizing total hepatic dose to preserve liver function.

The major limitation of the present study was the small number of subjects. A larger study population would provide a better picture of the clinical factors influencing the therapeutic outcome of SBRT.

What is already known on this topic?

SBRT is known as an effective treatment with acceptable toxicity rate for hepatic cancer. However, data of its use in Thai population is still lacked.

What this study adds?

This paper describes our experience of the outcome of SBRT in a Thai population from Chulabhorn hospital. Predictive factors for treatment response after SBRT could guide clinicians to make better decisions regarding treatment. However, the small number of patients in this study prevents meaningful interpretation of our data. Further study with a large population is required.

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Potential conflicts of interest

None.

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