Cyberknife stereotactic radiosurgery for patients with primary hepatocellular carcinoma

Byung Ock Choi¹, Ihl Bohng Choi¹,†, Hong Seok Jang¹, Young Nam Kang¹, Ji Sun Jang¹, Si Hyun Bae², Seung Kew Yoon², Gyu Young Chai³, Ki Mun Kang³, * .†

Address: ¹Department of Radiation Oncology, The Catholic University of Korea, School of Medicine, Seoul, South Korea, ²Department of Internal Medicine, The Catholic University of Korea, School of Medicine, WHO Collaborating College of Medicine, Seoul, South Korea, ³Department of Radiation Oncology, Gyeongsang National University, College of Medicine, Gyeongsang Institute of Health Sciences, Jinju, South Korea

Email: Byung Ock Choi- choibo67@catholic.ac.kr; Ihl Bohng Choi- ibchoi53@yahoo.co.kr; Hong Seok Jang-hsjang@catholic.ac.kr; Young Nam Kang-k3yn@catholic.ac.kr; Ji Sun Jang-spoulson@empal.com; Si Hyun Bae- shbae@catholic.ac.kr; Seung Kew Yoon-yoonsk@catholic.ac.kr; Gyu Young Chai-cgyinj@dreamwiz.com; Ki Mun Kang * -jsk92@gnu.ac.kr

* Corresponding author, † Equal contributors
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Abstract

Background: The objectives of this study was to evaluate the efficacy of Cyberknife stereotactic radiosurgery (SRS) for small non-resectable hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) in primary HCC.

Methods: Thirty one patients with HCC who were treated with Cyberknife SRS were used for the study. We studied 32 HCC lesions, where 23 lesions (22 patients) were treated targeting small non-resectable primary HCC, and 9 lesions (9 patients) targeting PVTT. Tumor volume was 3.6-57.3 cc (median, 25.2 cc) and Cyberknife SRS dose was 30-39 Gy (median, 36 Gy) in 3 fractions for consecutive days for 70-85% of the planned target volume.

Results: The median follow up was 10.5 months. The overall response rate was 71.9% [small HCC: 82.6% (17/23), PVTT: 44.4% (4/9)], with the complete and partial response rates of 31.3% [small HCC: 34.6% (8/23), PVTT: 22.2% (2/9)], and 40.6% [small HCC: 47.8% (11/23), PVTT: 22.2% (2/9)], respectively. No patient experienced Grade 4 toxicity.

Conclusion: Cyberknife SRS provides a feasible treatment modality with minimal side effects in selected patients with medically inoperable primary HCC.
Background

Primary hepatocellular carcinoma (HCC), which comprises 90% of all malignant cancers developed in the liver, is a fatal disease that causes death within a few months unless treated properly [1,2]. Many modalities such as surgical resection, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), external radiation therapy (RT) and transarterial chemoembolization (TACE) have been tried in the treatment for HCC [3-7], but the optimal treatment approach remains controversial. Currently, the conventional RT has a limited role for the treatment of HCC, because of the low efficacy of radiation for tumor control as well as the low tolerance of the liver to RT of tumoricidal dose [8]. With the conventional RT, it is not possible to deliver a high radiation dose to a treatment volume in a short time, without also irradiating some normal hepatic tissue. On the contrary, hypofractionated stereotactic radiosurgery (SRS) is a modality that can deliver a high dose of radiation in a short time to well defined hepatic tumor sites, and there is a rapid dose fall off gradient encompassing tumors.

SRS, for benign and malignant diseases, was initially used only for intracranial lesions. With the advent of advanced imaging techniques and robotic image-guided radiation technologies, the Cyberknife has extended highly conformal radiosurgery to extracranial SRS applications [9]. Cyberknife SRS is now being extended to more patients and clinical targets [10,11]. To date, there are only a few reports in the literature that assessed the response of HCC to SRS [12-14]. We have employed extracranial stereotactic RT, using the LINAC-based
radiosurgery system since 1995, with a special focus on liver tumors [15,16]. Expanding our experience further, we have attempted Cyberknife SRS alone for small primary non-resectable HCC, and used the combined therapy of TACE and SRS for advanced HCC with portal vein tumor thrombosis (PVTT). Therefore, we evaluated the response rate and toxicity of Cyberknife SRS for both small primary non-resectable HCC and advanced HCC with PVTT.

Methods

Patients eligibility
From March 2004 to March 2005, 31 patients participated in a retrospective study at the Cyberknife center, Catholic University. We treated 32 HCC lesions with the Cyberknife (Accuray Inc, Sunnyvale, CA) SRS, where 23 lesions (22 patients) were treated, targeting small non-resectable primary HCC, and 9 lesions (9 patients) targeting PVTT. The criteria for patients to be included in the study were as follows: (1) patients with histologically proven primary HCC, (2) patients not showing extrahepatic metastasis, (3) patients with tumor size (maximal diameter) ≤ 5 cm, (4) age < 75, (5) patients with HCC that did not develop within the transplanted liver, (6) patients who had ECOG score ≤ 3, (7) patients with no previous experience of radiotherapy and (8) patients with leukocytes ≥ 4,000/μl, platelet ≥ 50,000/μl. Written informed consent was obtained from all patients before therapy.

Treatment and dose prescription
In terms of previous treatment before SRS, 17 of our patients had received
TACE, 3 patients PEI, 6 patients RFA, and 5 patients had not received any previous treatment. TACE (range: 1 - 4 times, median: 2 times) was performed after SRS in patients with PVTT, whereas the patients in small HCC were treated with SRS alone. The interval between TACE and SRS was at least 2 weeks.

Stereotactic radiosurgery treatment was administered using the Cyberknife image guided radiosurgery system. The radiation dose was prescribed at the isodose line that could completely cover the hepatic tumor. Gross tumor volume (GTV) was defined as the tumor volume, which enhanced contrast at computer tomography (CT) scan, and planned target volume (PTV) included GTV with a 0.5 cm-margin. The total doses administered were 30-39 Gy (median, 36 Gy) with the prescription isodose level range of 70-85% (median, 80%) in 3 fractions over three consecutive days.

**Cyberknife SRS procedure and breath-holding technique**

Frameless extracranial radiosurgery was carried out at our institution using the Cyberknife SRS system. Liver parenchyma around the tumor was implanted with four gold markers, which acted as radiographic landmarks for the image guidance system. The fiducials were 1 × 3 mm gold seeds, which were implanted percutaneously using an 18-gauge needle under ultraonography guidance. In image-guided radiosurgery, the tumor position during treatment is always defined relative to the abdominal CT. Patients were positioned supine on the table. Images were taken in the spiral mode using 2 mm slice thickness. The
CT image was taken when breathing from the patient reached the maximum expiration. The Cyberknife SRS On-target treatment planning system (version 3.3) provided a wide range of treatment options, including the ability to use forward or inverse treatment planning associated with single-isocenter, multiple-isocenter, or conformal shape non-isocentric algorithms. In this study, the conformal shape inverse planning was used. Treatment was delivered in the step, image and shoot sequence. First, the robot positioned the linear accelerator at a fixed beam-pointing position. Then, the patient took a breath and held it while the imaging system acquired the targeting data. The patient then took a resting breath, followed by an RT breath-hold, during which the treatment beam was turned on. Anywhere from 10 to 50 monitor units of RT were delivered at each beam position, broken up into breath-holding periods of 10-15 sec, depending on the pulmonary capacity of the patient. Once the complete dose for a particular beam direction had been delivered, the robot advanced the LINAC to the next beam position and the imaging/treatment cycle was repeated. The beam pointing during each RT breath-hold was based on the tumor position observed during the most recent prior imaging during a breath-hold.

All patients were treated using the breath holding techniques as follows: the initial time from ‘breath-hold: inhale or exhale’ to ‘image acquisition for target localization purposes’ is 15 sec. The patient then breathes normally for 15-20 sec for ‘breath-hold: inhale or exhale’ and ‘SRS beam on’, followed by a third 15-20 sec for ‘breath-hold: inhale or exhale’, ‘a skin marker check’ and finally
‘Cyberknife beam on’. The position of the internal fiducials is then correlated with the movement of the chest wall and the robot retargets the linear accelerator accordingly in real time.

**Dose limitation to normal tissues**

The liver, stomach, duodenum, intestine, kidney, and spinal cords were contoured during the planning process and dose-volume histograms (DVH) were used to ensure that normal tissue tolerances were not exceeded.

**Liver**

Doses of 30-35 Gy with conventional fractionation are often considered to be the limit of liver tolerance. Kazunari Yamada et al. reported that the volume of the liver receiving a dose in excess of 30 Gy, with conventional fractionation, could be used as a predictive test for damage in liver function [17]. A V30 of < 50% is similar to the surgical criteria for lobectomy [18]. We evaluated V20 as a predictor for liver damage accrued from the SRS treatment in our study: in the α/β ratio of 3, 30 - 35 Gy with conventional fractionation is equivalent to a dose of 3 x 6 Gy (total, 18 Gy). The V20 was limited so as not to exceed 50% of the functional liver tissue.

**Stomach, duodenum and intestine**

Due to the lack of clinical data on the effect of very high fraction doses exceeding 8 Gy, the dose of 7 Gy was chosen based on the experience in brachytherapy [19]. Therefore, the maximum dose to the stomach, duodenum,
small or large bowel was limited to below 7 Gy per fraction (total, 21 Gy) to avoid serious side effects.

**Kidney**
Emani et al. suggested 23 Gy for TD5/5 for whole-kidney irradiation [20]. Cassady reported that a threshold dose of 15 Gy delivered with conventional fractionation appeared reasonable [21]. As renal toxicities are usually related to the total volume of treated kidney, DVH are essential to predict renal toxicities. In this study, at least 2/3 of the right kidney was limited to receive a dose of less than 5 Gy per fraction (total, 15 Gy): in the α/β ratio of 3, 23 Gy with conventional fractionation is equivalent to a dose of 3 x 5 Gy (total 15 Gy).

**Spinal cord**
The maximum dose to the spinal cord was limited to below the 7 Gy per fraction from the linear-quadratic formula of Withers et al: for an α/β ratio of 3, 42 Gy with conventional fractionation is equivalent to a dose of 3 x 7 Gy (total, 21 Gy) [22].

**Response and toxicity evaluation**
The tumor response was based on the change in the maximum tumor size on the abdominal CT scans 1 month after completion of SRS, and then tumor response was checked at 2–3-month intervals. A complete disappearance of the tumor was defined as complete response (CR), a decrease of more than 50% of the tumor size as partial response (PR), a decrease of less than 50% of the
tumor size or no change as stable disease (SD), and in-field progression with a tumor size increase of more than 25% as progressive disease (PD). Toxicity was evaluated according to the NCI common toxicity criteria (CTC 2.0 version) [23].

Results

Patients characteristics

Pretreatment characteristics of patients and tumors are summarized in Table 1. The median age was 59 years (range, 44-74 years), and males were predominant. The general condition of most patients was good, with 24 patients having ECOG scores of 0-1. The median target volume was 25.2cc (range, 3.6-57.3cc), 23.5cc (range, 3.6-57.3cc) in small HCC and 32.8cc (range: 3.9-47.7cc) in PVTT.

The median follow-up for 31 patients was 10.5 months (range, 2.0-18.5 months), 11.5 months (range, 2.0-18.5 months) in small HCC and 8.5 months (range, 2.0-14.5 months) in PVTT. The summary of Cyberknife SRS of patients is shown in Table 2.

Tumor response to treatments

The overall response rate (CR plus PR) was 71.9% (23/32) [small HCC: 82.6% (17/32), PVTT: 44.4% (4/9)]. Of the 32 lesions, 10 (31.3%) had a CR [small HCC - 34.8% (8/23), PVTT - 22.2% (2/9)] and 13 (40.6%) a PR [small HCC -
47.8% (11/23), PVTT – 22.2% (2/9). SD disease was documented in 9 (28.1%) lesions [small HCC: 17.4% (4/23), PVTT: 55.6% (5/9)]. (Table 3) Figure 1, 2 shows the result for patients who were classified as CR. Local recurrence was observed in 3 lesions, observed in small HCC (1) and PVTT (2). At the time of analysis, 3 patients had died of disease and 28 patients were alive.

**Toxicity**

Effects of toxicity associated with the treatment are shown in Table 4. The most common side effects were gastrointestinal toxicity in 15 patients. Twelve patients showed abnormal liver functions. In addition, hematological toxicity showed up as leukopenia in 8 patients and thrombocytopenia in 7 patients. These toxic effects were transient, and most of the patients recovered with medication. No patient suffered Grade 4 toxicity.

**Discussion**

Surgical resection has been considered the treatment of choice for long-term control of the HCC. However, less than 20% of patients are surgical candidates at diagnosis. In recent years, a number of alternative local modalities including PEI, TACE and RFA have been developed. These local treatments have shown local control rates of 86% after PEI [4], local control rates for liver metastasis of 70% after RFA [5] and 55% after TACE [6]. Seong JS et al. studied the combination of conformal RT with TACE for HCC and local control rates of 66% have been reported in patients [24]. As a result of our study, the local
control rate was observed to be 71.9%, which is at least equivalent to the invasive local therapies. Therefore, considering the quality of life during and following treatment and the noninvasive, painless approach associated with SRS, this technique may be a preferred treatment modality for primary HCC.

Conventional RT can reduce the probability of normal tissue complication, especially for late reacting normal tissue. Clinically, the biologic advantage of a larger volume of potential normal tissue repair, such as that occurs with conventional RT, is of particular importance when the safety margin is small between tumor and normal tissue. If the irradiated volume is restricted to the tumor with a very small security margin, sublethal damage repair is not a first-line aim because complete cell damage is intended. SRS can create a high-gradient dose falloff in the target tumor with a very small security margin.

Dose escalation appears to be a very important issue for local control rates. If HCC is treated with RT alone, it requires normal liver tissue-sparing radiation techniques, because the tolerance dose of the liver declines with the volume irradiated [25]. However, dose escalation with conventional RT is limited by prolonged treatment time (accelerated tumor cell repopulation) and increase of the dose to the functional liver tissue (impairment of liver function). SRS can deliver a high dose of radiation to the target tissue with a high degree of precision within the body [26], while sparing most of the adjacent organ, resulting in potentially better local control and lower risk for RT toxicity.
Published clinical data on extracranial SRS, especially for liver tumors, is limited [12-14]. Blomgren et al. published the first experiences of use of stereotactic RT for liver tumors [27]. They recommend a hypofractionated RT approach with an inhomogeneous dose distribution in the target. Herfarth KK et al. used a stereotactic single dose RT approach in the treatment of liver tumors [12]. In these studies, both demonstrated high local tumor control rate and low morbidity. The present study on Cyberknife was attempted based on the results from the above researches, and the results of this study confirmed that Cyberknife SRS is indeed helpful in the medically inoperable cases of small HCC.

The presence of PVTT is an extremely poor prognostic factor, because it can lead not only to, the wide dissemination of tumors throughout the liver due to the presence of arterioporal shunting, but also to marked worsening of the liver function as a result of decreased portal flow. In patients with PVTT, TACE was considered a contraindication because it could theoretically result in hepatic damage resulting from hepatic ischemia [28]. Moreover, no survival benefits have been observed in at least two randomized trials of TACE for patients with PVTT [29,30]. Tazawa et al. reported a retrospective study of combined therapy (local RT + TACE) in 24 patients with PVTT [31]. In their study, the survival rate was significantly better in the responders than the non-responders. However, Yamada et al. reported 19 patients who had combined therapy (local RT + TACE) with PVTT; They found no significant difference in overall survival between the responders and non-responders [17]. However, one significant finding in this study was that on follow-up angiograms, the protrusion of PVTT
into the main portal trunk decreased in all cases. Combined therapy (local RT + TACE) may prevent PVTT from spreading to the main trunk, suggesting a further benefit of TACE. Because the time frame for the RT period in this study was at least 6 weeks, in many cases, the tumor outside the RT fields continued to be enlarged after RT. A more short-term fractionation regimen may have prevented this problem. Our policy, in combining RT with TACE, was to use Cyberknife SRS solely to treat PVTT in a short treatment time, whereas intralobar HCC was treated with TACE. Cyberknife SRS, for primary HCC with PVTT, has shown acceptable local control.

In our study, we observed three patients with local recurrence in tumor of left hepatic lobe of the liver. Two of them were most likely due to a low radiation dose. The other patient had 2 lesions treated at one week intervals. One of 2 lesions showed complete response, the other showed local progression, with liver necrosis near the tumor. This appears to have resulted from inaccurate treatment of a moving target. The magnitude of respiration-induced target motion can be as large as 2-3 cm, peak-to-peak. Various methods have been proposed to control or mitigate target motion. These include active or passive breath-holding techniques [32], respiratory gating [33] and 4 dimension or tumor tracking [34]. Breath-holding techniques, by either actively or passively suspending the patient’s respiration, allow treatment during this interval. A study examining intra- and interfraction reproducibility of diaphragm position within a fraction can be reproduced satisfactorily. However, daily imaging and repositioning are still required in order to achieve any appreciable reduction in
treatment margin for precise treatment. Therefore, we suggest the other options, respiration-gating methods or 4 dimension methods.

**Conclusion**

Our study shows that Cyberknife SRS seems feasible and effective for medically inoperable primary HCC and PVTT. Further study is necessary to define the role of dose administered as well as fractionation and side effects in selected patients with medically inoperable primary HCC and PVTT.

**Competing interests**

The author(s) declare that they have no competing interests.

**Authors’ contributions**

BOC, IBC, HSJ, YNK, JSJ, SHB, SKY, GYC and KMK have made substantial contributions to conception and design of the study. BOC, IBC, HSJ, SHB, SKY and KMK carried out acquisitions of data. BOC, IBC, HSJ, YNK, JSJ, GYC and KMK carried out analysis and interpretation of data. BOC, IBC, HSJ, GYC and KMK have been involved in drafting the manuscript.

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Figure 1.
Figure 2.
Legends of Figure

**Figure 1**
(a) The initial abdominal CT scan with the primary HCC indicated by the arrow.  
(b) CT scan five months after SRS: CR follow-up status. (SRS, stereotactic radiosurgery)

**Figure 2**
(a) The initial angiogram with the PVTT indicated by the arrow.  
(b) Angiogram two months after SRS and three courses courseof TACE: CR follow-up status.  
(SRS, stereotactic radiosurgery)
Additional files provided with this submission:

Additional file 1: 20080306 cyberknife srs for hcc tables 1-4.doc, 97K
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