Int J Clin Exp Med 2017;10(2):3272-3280
www.ijcem.com /ISSN:1940-5901/IJCEM0024524

*Original Article*

# Clinical effects and prognostic factors of gyro knife radiotherapy in patients with hepatocellular carcinoma

Yayun Cui[1*], Hong Zhu[2*], Mingming Fang[3], Yiting Tang[3], Judong Luo[3], Liting Qian[1*]

*[1]Department of Radiation Oncology, The Affiliated Provincial Hospital of Anhui Medical University, Hefei, China; [2]Department of Radiation Oncology, Minhang Branch of Cancer Hospital of Fudan University, Shanghai, China; [3]Department of Radiation Oncology, Changzhou Tumor Hospital, Soochow University, Changzhou, China. [*]Equal contributors.*

Received January 20, 2016; Accepted August 2, 2016; Epub February 15, 2017; Published February 28, 2017

**Abstract:** Purpose: We evaluated the short-term effects of cobalt-60 gyro rotating stereotactic radiotherapy (gyro knife) for primary hepatocellular carcinoma (HCC) ineligible for local therapy or surgery. Methods: Between August 2010 and December 2014, gyro knife radiotherapy was used in our department of radiation oncology to treat 63 patients with HCC who met the inclusion criteria and were unable or unwilling to undergo surgery. Patients were aged 58 years on average, and the mean radiation dose was 3614.84 cGy. The short-term effects, side effects, survival time, and prognostic factors were analyzed after treatment. Results: At follow-up 3 months after radiotherapy, there were 29 complete response patients, 23 partial response patients, nine stable disease patients, and two progressive disease patients, accounting for an overall response rate of 82.5%. The local control rate after a 1-year follow-up was 84.1%. There were no grade 4 hematologic, gastrointestinal, or hepatic toxicities. The half-year, 1-year, and 2-year survival rates of patients were 83.9% (51/63), 54.8% (30/63), and 20.2% (7/63), respectively, with a median survival time of 450 days (15 months). In the univariate analysis of the test group, survival was significantly associated with Eastern Cooperative Oncology Group (ECOG) score, longest tumor diameter, portal vein tumor thrombosis, total dose, Child-Pugh class of liver function, and AJCC stage ($P<0.05$). The multivariate analysis showed that ECOG ($P = 0.012$, Wald = 6.292) and Child-Pugh class of liver function ($P = 0.000$, Wald = 34.602) significantly correlated with overall survival. Conclusions: Our study suggests that gyro knife treatment is a very safe and effective treatment option for HCC patients.

**Keywords:** Hepatocellular carcinoma, gyro rotating stereotactic radiotherapy, prognostic factors

## Introduction

Hepatocellular carcinoma (HCC) is the most common primary carcinoma of the liver. It is one of the most rapidly increasing cancers in terms of incidence and mortality, globally and in China [1, 2]. The mortality of HCC ranks third of all tumors worldwide [3]. Fewer than 30% of patients are eligible for currently available curative treatments, namely liver transplant, surgery, and radiofrequency ablation (RFA), as a result of disease stage, poor liver function, or limited resources [4]. Therefore, a significant proportion of patients are incurable, with a 1-year survival rate ranging from 20% to 30% [5-7]. Transarterial chemoembolization (TACE) increases survival primarily in patients without major vascular thrombosis [8, 9]. However, TACE has a high recurrence rate and a poor long-term effect. In patients unsuitable for TACE, sorafenib can increase 1-year survival, from 30% with best supportive care to 45% [5, 6]. Unfortunately, progression of the treated lesions or elsewhere in the liver is almost invariable for patients treated with TACE or sorafenib.

Before the 1990s, primary HCC patients were less likely to receive radiotherapy because of the poor radiation tolerance and great damage to normal liver. To our knowledge, the liver belongs to late-responding tissue and represents a typical organ associated with the radiation volume effect. The radiation tolerance dose is associated with radiation volume, radiation times, and each radiation dose as well as the irradiated dose of normal liver tissue. With

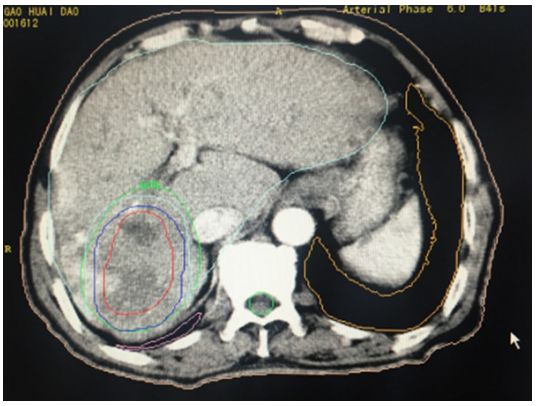

**Figure 1.** Gross tumor volume (red), planning target volume (blue), and 50% isodose lines (green) of primary hepatocellular carcinoma.

the application of stereotactic body radiotherapy (SBRT), normal liver tissue can be protected to a higher degree during the treatment of liver tumors. SBRT highlights the advantages of precise targeting and little adverse reaction in patients with poor health and intolerance to surgery due to various reasons. For the treatment of HCC, there have been numerous trials assessing and analyzing the feasibility and effect of SBRT [10-13, 14-16]. In recent years, cobalt-60 gyro rotating stereotactic radiotherapy (gyro knife) has emerged as the world's most advanced precise radiotherapy equipment.

Therefore, between August 2010 and December 2014, we used gyro knife radiotherapy in our department of radiation oncology to treat 63 patients with HCC who met the inclusion criteria and were unable or unwilling to undergo surgery. Clinical efficacy, side effects, survival time, and prognostic factors were analyzed after treatment.

## Materials and methods

### *Case information*

Between August 2010 and October 2014, we admitted approximately 100 patients with unresectable primary HCC. All the patients were judged inoperable or inaccessible by a team consisting of a hepatobiliary surgeon, radiologist, and hepatologist. Among them, only 63 patients met the inclusion criteria. All the enrolled cases were diagnosed as primary HCC by contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), or alpha-fetoprotein (AFP) tumor marker test or by percutaneous biopsy of hepatic masses (forty-five patients confirmed by pathological biopsy). Among the 63 enrolled patients, there were 54 men and 9 women, aged 31 to 82 years, with an average age of 58 years. The Eastern Cooperative Oncology Group (ECOG) scores ranged from 0 to 3 points. Most patients ranked Child-Pugh class A or B for liver function, while a small portion of Child-Pugh class C was also enrolled. Hepatic tumors were single or multiple and clustered in one site, with fewer than three lesions. Patients had aspartate and alanine aminotransferase of <100 μ/l, with no significant myelosuppression or renal impairment and no obvious jaundice or ascites. Patients had no surgical indications or unwillingness to surgery and were intolerant to or refused hepatic arterial chemoembolization. According to the American Joint Committee on Cancer TNM staging for HCC, 34 cases were stage I, eight cases were stage II, 17 cases were stage III, and four cases were stable IV.

### *Treatment*

The treatment was performed using a gyro knife, the GMX-I gyro rotating cobalt-60 stereotactic radiotherapy system (Gammastar, Shanghai, China). The treatment procedure was as follows: (1) Patient was fixed on a treatment table using a stereotaxic frame. A supine position was used in the eupneic status and hands crossed behind head. Intravenous contrast-Enhanced helical CT was performed 10 min after administration of an oral contrast agent (150-200 mL). Slice thickness was 5 mm. Scan range covered 3-5 cm above the dome of the diaphragm and the lower pole of the right kidney. CT images were used to design the stereotactic radiotherapy treatment planning system through the network input planning system. (2) A 3-dimensional (3D) planning system was used for planning and implementing the treatment. The procedure was as follows: ① Delineation of patient's body surface, vital tissues and organs and reconstruction of target regions: The gross tumor volume (GTV) was sketched according to CT or MRI images, and full consideration was given to errors in respiratory motion and secondary positioning. Finally, planning target volume (PTV) margins were determined: 1 cm in the left/right and anterior/posterior directions, and 1.5 cm in the cranial/

**Table 1.** Toxicity, CTCAE v4.0

| Toxicity | Grade 0 (%) | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) | Grade 4 (%) |
|---|---|---|---|---|---|
| Hematologic toxicity | 40 (63.5) | 12 (19.0) | 9 (14.3) | 2 (3.2) | 0 (0) |
| Gastrointestinal reaction | 31 (49.2) | 17 (27.0) | 13 (20.6) | 2 (3.2) | 0 (0) |
| Liver function abnormality | 21 (33.3) | 23 (36.5) | 15 (23.8) | 4 (6.4) | 0 (0) |

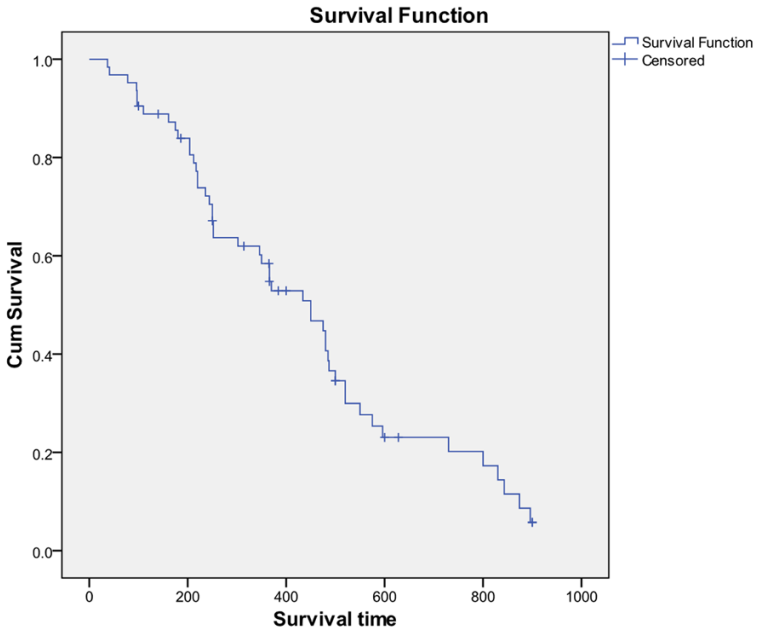


**Figure 2.** Survival curve.

caudal directions. The treatment plans were comprehensively evaluated and optimized using dose volume histogram (DVH) and isodose line. And 90-95% of the PTV should be covered by the 50% isodose line (**Figure 1**). ② Design of gamma knife conformal radiotherapy treatment planning: The shape of the radiation field was designed through the beam's eye view, ensuring the target volume within the radiation field. For the tissue of vital organs, such as the stomach, duodenum, pancreas, kidney, and spinal cord, the irradiated dose of normal liver tissue was V30 ≤33%, and the remaining was controlled within the range of tolerance dose. ③ Optimization of radiotherapy treatment planning: The treatment plans were comprehensively evaluated and optimized using DVH and the isodose line. ④ The patients were treated with a total radiation dose of 1800-5670 cGy. The mean dose was 3614.84 cGy, and single doses ranged between 240 and 500 cGy. Irradiation was performed 5 times a week and was completed in 2 to 3 weeks. The patients received positive liver-protecting, stomach-protecting and symptomatic supportive treatment during radiotherapy.

*Efficacy evaluation*

Patients underwent dynamic CT scans or MRI before treatment and 3 months after completion of SBRT, and then, tumor response was checked at 2-3 month intervals. Treatment response and local recurrence were evaluated using follow-up dynamic CT scans and serum AFP. MRI scans and/or positron emission tomography (PET) CT scans were used to discriminate the vague lesion or response and evaluate overall response in some cases. Whole body check was performed once every 3 months in the first 2 years and once every 6 months after 2 years. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors 1.1 published by the World Health Organization. The evaluation criteria 3 months after completion of SBRT were as follows: complete response (CR)-complete tumor regression maintained for at least more than 4 weeks, with no emergence of new lesions; partial response (PR)-≥50% tumor volume regression maintained for at least 4 weeks, with no emergence of new lesions; no change (NC)-<50% regression or >25% growth of tumor volume; and progressive disease (PD)->25% tumor volume growth or emergence of new lesions. CR + PR was defined as responsive. Radiation complications were evaluated according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) criteria and graded using the National Cancer Institute Common Terminology Criteria (CTCAE v4.0).

*Methods*

All patients successfully completed the treatment plans and were followed up. Overall sur-

**Table 2.** Univariate survival analysis (log-rank test)

| Factor | n (%) | *P* value | $\chi^2$ value |
|---|---|---|---|
| Age/year | | 0.193 | 1.692 |
| ≤60 | 34 (54) | | |
| >60 | 29 (46) | | |
| Gender | | 0.990 | 0.000 |
| Male | 54 (85.7) | | |
| Female | 9 (14.3) | | |
| ECOG | | 0.000 | 103.51 |
| 0 | 8 (12.7) | | |
| 1 | 31 (49.2) | | |
| 2 | 17 (27.0) | | |
| 3 | 7 (11.1) | | |
| Hepatitis B virus | | 0.385 | 0.756 |
| + | 39 (61.9) | | |
| - | 24 (38.1) | | |
| No. of tumor | | 0.828 | 0.047 |
| 1 | 58 (92.1) | | |
| 2 | 5 (7.9) | | |
| Alpha-fetoprotein (IU/ml) | | 0.233 | 1.420 |
| ≤200 | 30 (47.6) | | |
| >200 | 33 (52.4) | | |
| Longest diameter | | 0.000 | 29.410 |
| ≤5 | 20 (31.8) | | |
| 5-10 | 21 (33.3) | | |
| ≥10 | 22 (34.9) | | |
| Chemo | | 0.337 | 0.923 |
| Yes | 5 (7.9) | | |
| No | 58 (92.1) | | |
| Portal vein tumor thrombosis | | 0.005 | 7.710 |
| Yes | 13 (20.6) | | |
| No | 50 (79.4) | | |
| Interventional therapy | | 0.457 | 0.552 |
| Yes | 31 (49.2) | | |
| No | 32 (50.8) | | |
| Irradiation dose | | 0.029 | 9.043 |
| ≤30 | 25 (39.7) | | |
| >30, ≤40 | 16 (25.4) | | |
| >40, ≤50 | 19 (30.1) | | |
| >50 | 3 (4.8) | | |
| Liver function | | 0.000 | 125.980 |
| Child A | 42 (66.7) | | |
| Child B | 16 (25.4) | | |
| Child C | 5 (7.9) | | |
| AJCC stage | | 0.000 | 23.924 |
| I | 34 (54.0) | | |
| II | 8 (12.7) | | |
| III | 17 (27.0) | | |
| IV | 4 (6.3) | | |

vival rate was calculated with the start date of gyro knife radiotherapy as the beginning of survival time. The patients were followed by telephone and regular visits. The follow-up ended at the end of June 2015. The long-term effect was assessed using the 1-year and 2-year survival rate. The follow-up rate was 100%, and the follow-up time was 12-50 months.

*Statistical analyses*

In the test group, univariate analyses of survival were performed with the Kaplan-Meier method and the log-rank test. Those prognostic factors that were significant in the univariate analysis ($P<0.05$) were additionally evaluated in a multivariate analysis, which was performed with the Cox proportional hazards model. Analyses were performed using IBM Statistics Data Editor, version 19.0.

## Results

*Short-term effect*

At a follow-up 3 months after the completion of radiotherapy, there were 29 CR patients, 23 PR patients, 9 NC patients, and 2 PD patients; the overall response rate (RR) of the 63 patients was 82.5%. After 1-year follow up, lesions were not controlled in the local irradiated site for 10 patients, and the local control rate was 84.1%. Regarding the reduction of AFP, the pre-treatment mean value was 1291.32 ± 562.53 ng/mL, and the post-treatment mean value was 517.46 ± 77.99 ng/mL; a paired t-test revealed no statistically significant difference between the pre-treatment and post-treatment values ($P = 0.159$).

*Short-term toxicity*

Toxicity after radiotherapy was assessed in accordance with CTCAE 4.0 standard. No grade 4 hematologic toxicity, gastrointestinal toxicity and liver function toxicity occurred and radiation related toxicity could be tolerated (**Table 1**).

*Survival time*

The half-year, 1-year, and 2-year survival rates of the patients were 83.9% (51/63),

**Table 3.** Multivariate COX regression analysis

| Factor | *B* | *SE* | *Wald* | *P* value | 95.0% *CI* | |
|---|---|---|---|---|---|---|
| ECOG | 0.587 | 0.234 | 6.292 | 0.012 | 1.137 | 2.846 |
| Child-Pugh class | 2.447 | 0.416 | 34.602 | 0.000 | 5.112 | 26.109 |

Forward stepwise regression based on maximum likelihood estimation (Forward: LR).

54.8% (30/63) and 20.2% (7/63), respectively. Median survival time was 450 days (95% confidence interval: 330.639-569.361) or 15 months (**Figure 2**).

*Univariate analysis*

In the univariate analysis of the test group, survival was significantly associated with ECOG, longest diameter, portal vein tumor thrombosis, total dose, Child-Pugh class of liver function, and AJCC stage (P<0.05; **Table 2**).

*Multivariate analysis*

The multivariate analysis showed that ECOG (P = 0.012, Wald = 6.292) and Child-Pugh class of liver function (P = 0.000, Wald = 34.602) significantly correlated with overall survival (**Table 3**).

## Discussion

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, and its incidence is on the rise. The primary therapy is resection or liver transplant, but only a minority of patients present with resectable disease [17]. RT for the treatment of unresectable HCC has been attempted for more than 4 decades. The study of liver cancer radiotherapy shows that HCC cells are sensitive to radiation, with $\alpha/\beta$ >11; thus, HCCs are radiation-sensitive tissues, equivalent to poorly differentiated squamous cell carcinoma [18]. Historically, radiotherapy has not played a significant role in the treatment of liver malignancies because of the low tolerance of the whole liver to radiation. In early trials involving the use of whole-liver RT, generally in combination with intra-arterial and/or intravenous chemotherapy, the reported 2-year survival rate was <10% [19]. With improvements in 3D conformal radiotherapy and intensity-modulated radiotherapy, higher doses of radiation can be delivered to target region with low doses to the noninvolved liver; thus, experience in the use of radiation for the treatment of focal HCC has increased. At the same time, our understanding of the relationships between radiation dose and volume and the risk of classic radiation-induced liver disease and other toxicities more likely to occur in HCC patients has improved considerably. These developments have led to a body of evidence that now supports the careful use of radiotherapy for unresectable HCC [17].

With regard to the application of SBRT, domestic and foreign studies have reported good effects of X-ray SBRT in the treatment of liver cancer; local control and survival rates are higher than those obtained by previous radiotherapies [10-13]. In the present study, SBRT was performed using the new gyro rotating cobalt 60 stereotactic radiosurgery system, referred to as “gyro knife”. This system is a new stereotactic and precise radiotherapy device for the treatment of systemic tumors. Gyro knife uses the principle of multi-source rotating focus, “gyroscope peak”, which concentrates γ-rays in a geometric focus to irradiate the preselected target in the body. In this way, the lesion is subjected to high-dose radiation, while the surrounding normal tissues are subjected to low-dose radiation. Within a certain range of volume, a local radiation dose is sufficient to kill tumor cells without affecting the surrounding normal tissue. The treatment process is generally identical to that of previous gamma knife treatment, including four steps of positioning, planning, repositioning, and irradiation, respectively. Gyro knife enables accurate positioning on helical CT, with a minimal allowable error. This method maximizes the range of incident path by one time of static focus and two times of rotating focus of γ-rays. This increases the focus-skin ratio to a greater degree and allows for accurate and concentrated irradiation on the focus in the tumor target volume. The radiation dose actually received by the tumor exceeds the dose distribution characteristics of present 3D conformal linear accelerators and gamma knife treatment. Furthermore, the radiation dose received by normal tissue surrounding the lesion decreases rapidly, thereby playing a good role in protecting vital organs around the tumor. Compared with conventional gamma knife, the greatest advantages of gyro knife include high irradiation accuracy and radi-

**Table 4.** Published studies of stereotactic radiation therapy for HCC

| Study year | Treatment | Study type | Number | Tumor size median (cm) | RT dose (Gy) | Local control (%) | Overall survival (%) | Median survival months |
|---|---|---|---|---|---|---|---|---|
| Cardenes 2010 [21] | CyberKnife | Phase I | 25 | 4.0 | 36-48/3FX | 100% | 75% (1 year) 60 (2 year) | - |
| Dewas 2012 [22] | CyberKnife | Retrospective | 48 | 4.8 | Median 45 | 90.5 (1 year) | - | - |
| Jang 2013 [10] | SBRT | Retrospective | 108 | 3.0 | Median 51/3FX | 87% (2 years) | 63% (2 year) | - |
| Bujold 2013 [12] | SBRT | Phase I and II | 102 | 7.3 | Median 33/6FX | 87% (1 year) | 55% (1 year) | 17.0 |
| Present study | Gyro knife | Phase I | 63 | 5.95 | Median 36/6-10FX | 84.1% (1 year) | 54.8% (1 year) | 15.0 |

ation dose but low side effects of radiotherapy. Gyro knife effectively improves the control rate and killing effects of tumors. A few retrospective studies have reported that gyro knife radiotherapy can achieve excellent effects for the treatment of intermediate and advanced primary liver cancer as well as metastatic lymph nodes and portal vein tumor thrombosis [20].

Evaluation of the short-term effect revealed 29 CR patients, 23 PR patients, 9 NC patients, and 2 PD patients in the test group (63 patients), accounting for an overall RR (CR + PR) of 82.5%. The mean value of AFP, a tumor marker for liver cancer, obviously decreased after treatment; however, a paired t test revealed no statistically significant difference (P = 0.159). Additionally, univariate analysis did not reveal that AFP was a prognostic factor affecting overall survival time. Moreover, AFP did not show statistical significance in the univariate analysis of factors affecting local control and overall survival by Jiang et al. [10]. Similarly, Kwon et al. [11] assessed the association of tumors with AFP response and proposed that there was no significance between other patterns of final AFP response and tumor progression type.

Regarding the short-term toxicity, 12.9% of patients showed grade 3 hematologic toxicity (3.2%), gastrointestinal reaction (3.2%), or liver function abnormality (6.4%) after treatment, and none of them had grade 4 or higher toxicities. Won Il Jang [10] reported a study enrolling 108 HCC patients treated with SBRT: SBRT was delivered in three split courses, the median maximum diameter of tumor was 3.0 cm (range, 1.0-7.0 cm), and the median radiation dose was 51 Gy (range, 33-60 Gy). At 3 months after the completion of SBRT, 5 patients (6%) showed grade 3 or 4 gastrointestinal toxicity; 4 (5%) showed non-classical RILD, and 3 of them were inversed during a long-term follow-up; 1 (1%) experienced grade 3 hyperbilirubinemia. Additionally, a study by Bujold et al. [12] enrolled 102 patients with liver cancer; SBRT was delivered in 6 split courses, and the SBRT radiation dose ranged between 24 and 54 Gy. In a long-term follow-up, 30% of the patients showed grade 3 toxicities. Taken together, the present study and other similar studies indicate that the toxicity of SBRT is within the range of tolerance when it is used for liver cancer radiotherapy.

Our patients had 1-year and 2-year survival rates of 54.8% and 20.2%, respectively; their median survival time lasted for 450 days, or 15 months (**Table 4**). In other similar studies, the 1-year survival rates vary from 55% to 75% [10, 12, 21, 22], slightly higher than our results. After 1-year follow-up, our patients obtained a local control rate of 84.1%. In other series in the literature, rates of local control vary from 87% to 100%, still slightly higher than our results. Comparing all the data sets, we inferred that the lower results were related to larger liver tumor lesions and lower radiation dose in our patients compared with those in other similar studies.

However, improved local lesion control of patients does not necessarily mean improved survival. The effect on survival is difficult to explain in the presence of other factors. Therefore, it is necessary to analyze relevant prognostic factors. In the univariate analysis of the test group, survival was significantly associated with ECOG, longest diameter, portal vein tumor thrombosis, total dose, Child-Pugh class of liver function, and AJCC stage (P<0.05; **Table 2**). The multivariate analysis showed that ECOG (P = 0.012, Wald = 6.292) and Child-Pugh class of liver function (P = 0.000, Wald = 34.602) significantly correlated with overall survival (**Table 3**).

In foreign countries, SBRT has been used to treat liver cancer, and some studies have analyzed the prognostic factors. Bujold et al. [12] enrolled 102 patients with HCC undergoing SBRT; the SBRT dose varied in the range of 24-54 Gy, radiotherapy frequency was 6 times, and a median survival time of 17.0 months was obtained by follow-up. Univariate analysis showed that tumor vascular thrombosis and GTV volume were 2 factors affecting overall survival, whereas multivariate analysis indicated that tumor vascular thrombosis was a major factor. Additionally, Kwon et al. [11] enrolled 42 patients who had tumor volumes ≤100 CC and underwent SBRT at 30-39 Gy/3 times. The 1-year and 3-year overall survival rates were estimated to be 92.9% and 58.6%, respectively. When analyzing the factors affecting survival, univariate analysis indicated that the initial infield response to treatment, infield progression, tumor volume <32 cc, and Child-Pugh score affected survival; multivariate analysis revealed that tumor volume <32 cc and distant metastasis or not affected survival. Jang et al. [10] enrolled 108 patients with HCC who underwent SBRT, and multivariate analysis revealed that SBRT dose (P = 0.005) and Barcelona Clinic Liver Cancer stage (P = 0.015) were significant factors influencing overall survival. However, the significant factors in a univariate analysis (i.e., the longest diameter of tumor and the number of courses of previous TACE treatment) did not show significance in multivariate analysis. Furthermore, a similar study has suggested that the longest tumor diameter and SBRT dose affected survival [23]. More recently, in a multivariate analysis, female gender, a BCLC B-C stage, a sum of all lesions with diameters of ≥2 cm, and a previous treatment were independent prognostic factors of overall survival [24]. To date, studies have included different factors in analyses with a relatively small sample size, leading to a lack of uniform standards for factors influencing HCC survival.

In recent years, a novel therapeutic approach of SBRT combined with TACE has obtained good results in the treatment of intermediate and advanced liver cancer [25-27]. The treatment regimen of TACE combined with SBRT effectively uses the anti-tumor mechanisms of both the methods. TACE blocks blood supply to tumors, leading to severe ischemic necrosis and shrinkage of the tumor. On this basis, the application of SBRT can reduce the required radiation dose and attenuate the damage to surrounding normal tissue; moreover, it uses radiation to degenerate vascular endothelial cells, block blood vessels, and prolong the retention time of drugs in the body, thereby enhancing the tumor-killing effect. Sorafenib is a targeted anti-tumor drug that can inhibit the RAF/MEK/ERK signaling cascade pathway and thereby suppress tumor cell proliferation. Meanwhile, sorafenib can inhibit vascular endothelial growth factor and platelet-derived growth factor receptor and block tumor neovascularization, thereby playing an anti-tumor effect. In the meantime, sorafenib can enhance tumor sensitivity to radiotherapy [28]. Whether sorafenib can be used in combination with SBRT to improve clinical efficacy is worthy of further exploration.

In conclusion, our study suggests that gyro knife treatment is a very safe and effective treatment option for HCC patients. This method provides good local control with a short treatment period and tolerated side effects. Further large multi-institutional prospective randomized controlled trials are required to further confirm the efficacy of gyro knife treatment in these patients.

## Acknowledgements

This work is supported by the Natural Science Foundation of Anhui (1608085QH215), Medical Scientific Program of Shanghai Health and Family Planning Commision (201540163), Jiangsu Provincial Scientific Program (BK20151174; BE2015631), Changzhou Scientific Program (CE20155046; CJ20159038; QN201503).

## Disclosure of conflict of interest

None.

**Address correspondence to:** Liting Qian, Department of Radiation Oncology, The Affiliated Provincial Hospital of Anhui Medical University, Hefei 230001, China. E-mail: money2004@sina.com

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