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Stereotactic body radiation therapy for the management of HCC

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Abstract

Hepatocellular carcinoma (HCC) is a common malignant tumor in China. After years of efforts, there has been great progress in the management of liver cancer, but overall, it is still not ideal. At present, there are many therapies for liver cancer, including surgical resection, transcatheter arterial chemoembolization (TACE), ablation, molecular targeted therapy, stereotactic body radiation therapy, chemotherapy, immunotherapy, and so on. Studies have reported that TACE combined with radiotherapy can shrink the tumor, and some of the remainder will be resectable, resulting in cure. For HCC with tumor thrombus, the tumor thrombus was reduced and then resected after neoadjuvant radiotherapy. The survival time of the patients with portal vein tumor thrombus was significantly longer than that of the patients without neoadjuvant radiotherapy. Large liver cancer will be reduced to small liver cancer after comprehensive treatment, which can be transformed into stereotactic radiotherapy or radiofrequency ablation, and can also be palliative to radical treatment. Individualized and multidisciplinary therapy for liver cancer is the direction of future development. More clinical evidence-based level of radiotherapy treatment of liver cancer should be done in the future.

Keywords: Hepatocellular carcinoma, stereotactic body radiation therapy, tumor thrombus, combined therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is a common malignant tumor that seriously endangers human health. At present, the main treatment for small HCC is surgical resection and radiofrequency ablation, but some patients are not suitable for surgery or radiofrequency ablation. In recent years, with the development of radiotherapy technology, the application of stereotactic body radiation therapy (SBRT) is increasing. Some retrospective studies have shown that its therapeutic effect on small liver tumors is equivalent to that of traditional surgery or radiofrequency ablation, and that it can also be used as a radical treatment



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for small liver tumors. Some patients with unresectable tumor thrombus can be converted to surgical resection after radiotherapy, and external radiotherapy can also be applied for bridging treatment before liver transplantation. A narrow margin with a distance of less than 1 cm from tumor resection edge is possible with radiotherapy after liver resection, to reduce local recurrence or distant metastasis of HCC and to prolong disease-free survival (DFS) of patients. The mechanism of killing tumor cell by SBRT may be different from conventional fractionated radiotherapy. With the increase of fractionated dose, double-strand DNA breaks increase, and the repair of sublethal damage decreases. Moreover, when the single fractionated dose is more than 8-10 Gy, the tumor vascular endothelial cells rapidly wither after 1-6 h of irradiation, and blood vessels are occluded, leading to a secondary tumor killing effect, which is mainly through the acid sphingomyelinase pathway-mediated apoptosis of vascular endothelial cells^[1-3], but conventional radiotherapy does not have the above effect. After conventional fractionated radiotherapy, tumor cell death is mainly achieved by cell apoptosis, while after high dose irradiation, tumor cell death is mainly in the form of “swelling death”^[4], and tumor cell membrane is destroyed, releasing tumor specific antigen, becoming “*in situ* tumor vaccine”, which can stimulate the immune system to kill residual tumor^[5].

EFFECT OF SBRT ON LIVER FUNCTION

Cárdenes *et al.*^[6] conducted a phase I clinical study of dose escalation in patients with liver cancer: patients with a tumor diameter less than 6 cm and Child-Pugh (CP) Class A could tolerate 48 Gy in three fractions, and the patients with CP class B could not tolerate 42 Gy in three fractions, while no adverse effects occurred after adjustment to 40 Gy in 5 fractions. The CP score was the only risk factor related to hepatotoxicity or death within six months of SBRT treatment ($P = 0.03$). Three patients had classic radiation-induced liver disease, all of which were above CP class B7. We believe that good liver function was needed for SBRT treatment of liver cancer. Furthermore, CP score must be ≤ 7 , and patients with CP score > 8 have high risk of liver failure after SBRT treatment.

SBRT FOR PRIMARY LIVER CANCER

Many studies in the literature have focused on the study of liver cancer lesions with the diameter of less than 6 cm. The 1- and 2-year local control (LC) rates after SBRT were 72%-100% and 54.4%-100%, respectively, and the 1-year survival rates were 72.7%-100% and 45.3%-87.9%, respectively^[6-17], but the dose fractionation of radiotherapy used in various clinical studies was not the same. Patients with CP class A or tumor diameter less than 3 cm usually undergo irradiation more than 10 Gy each time, total for 3-5 times. Because of the good LC rates and tolerability, SBRT is recognized as an alternative for small liver tumors unsuitable for surgery. Yoon *et al.*^[7] applied SBRT to treat 93 cases of inoperable liver cancer with median diameter of 2 cm (1-6 cm), given 30-60 Gy or 10-20 Gy in 3-4 fractions, and the 1- and 3-year overall survival (OS) rates were 86 and 53.8%, respectively. LC failure was mainly seen in patients with liver cancer ≥ 3 cm, and the 3-year LC rates of liver cancer with diameter ≥ 3.0 , 2.1-3.0 and ≤ 2.0 cm were 76.3, 93.3 and 100%, respectively, the intrahepatic 3-year recurrence-free survival (RFS) rate was 32.4%. Six patients (6.5%) had \geq grade 3 hepatotoxicity. Similarly, Kwon *et al.*^[8] reported that 42 cases of liver cancer were treated with CyberKnife at a dose of 30-39 Gy in 3 fractions; the complete response (CR) rate was 59.6% and the partial response (PR) rate was 26.2%, while the 1- and 3-year OS rates were 92.9 and 58.6%, respectively. Kimura *et al.*^[9] used 48 Gy in 4 fractions to treat 65 patients with CP class A/B and median tumor diameter of 1.6 cm; 2-year OS, RFS and LC were 76, 40 and 100%. Fifteen patients (23%) had \geq grade 3 adverse reactions 6-12 months after SBRT, and the level ≥ 3 adverse reactions in CP class B were higher than those in CP class A ($P = 0.0127$)^[9].

There is no prospective study comparing SBRT with surgery or TACE in the treatment of primary liver cancer. Honda *et al.*^[15] applied sequential SBRT and TACE compared with TACE alone in the treatment of primary liver cancer with diameter less than 3 cm; of the 30 cases in the SBRT group, 29 cases (96.3%) had a CR, but only 1 in 38 cases in the TACE group had a CR (3.3%). There was no radiation-related injury in

Table 1. Studies of stereotactic body radiation therapy in hepatocellular carcinoma

Authors	Cases	CP class A/ B/C	Tumor diameter or GTV	Dose/times (Gy/ time)	CR/PR/SD (%)	1/2/3-year LC (%)	1/2/3-year OS (%)
Cárdenes <i>et al.</i> ^[16]	17	A6/B11	2-6cm or 8-95 cm ³	36-48/3;36-42/3;40/5	25/56/19	100/N/N	75/60/N
Yoon <i>et al.</i> ^[17]	93	A69/B24	1-6 cm	30-60/3-4	15.5/45.7/36.9	94.8/N/92.1	86/N/53.8
Kimura <i>et al.</i> ^[19]	65	A56/B9	0.5-5.4 cm ³	48/4 or 60/8	100/100/N	92.3/76/N	N
Andolino <i>et al.</i> ^[12]	60	A36/B24	1-6.5 cm	m44/m3;m40/m5	30/40/25	N/90/N	N/67/N
Takeda <i>et al.</i> ^[13]	63	A44/B19	1-5 cm	35-40/5	100/95/92	100/87/73	N
Park <i>et al.</i> ^[16]	26	A19/B7	1.1-5.7 cm	40-50/10	25/42.9/32.1	N/87.6/N	88.5/67.2/N
Yuan <i>et al.</i> ^[17]	22	A10/B10/C2	1.6-9.5 cm	39-54/3-8	50/41/9	92.9/90/67.7	N

CP: Child-Pugh Class; GTV: gross tumor volume; m: median; N: not applicable; CR: complete response; PR: partial response; SD: stable disease; LC: local control; OS: overall survival

the SBRT group. Another retrospective study compared CyberKnife with surgical resection in the treatment of stage I liver cancer; 22 cases were treated with SBRT, and 26 patients achieved R0 resection. There was no difference in 3-year survival rate (69.2% vs. 57.1%, $P = 0.49$). Although the sample size was limited, the authors believed that SBRT is effective in the treatment of early stage liver cancer and that the curative effect is not inferior to that of surgical resection^[17] [Table 1].

SBRT IN THE TREATMENT OF PORTAL/VENA CAVA TUMOR THROMBUS

Tumor thrombus is an unavoidable difficulty in the treatment of liver cancer. The tumor thrombus will aggravate the occurrence of portal hypertension, ascites, liver failure, intrahepatic and extrahepatic dissemination. Choi *et al.*^[18] analyzed the treatment of advanced liver cancer with portal vein tumor thrombus (PVTT) by SBRT combined with TACE; 9 cases with PVTT treated with TACE at a median dose of 36 Gy (30-39 Gy in 3 fractions), and after a median follow-up time of 10.5 months, achieved PVTT CR rate of 11.1% (1/9), PR rate of 33.3% (3/9), objective response rate (ORR) of 44.4% (4/9) and median OS of 8 months in advanced liver cancer^[18]. Xi *et al.*^[19] applied a median dose of 36 Gy in 6 fractions to treat primary liver cancer with portal/vena cava tumor thrombus, and 25 of 41 patients had received TACE, with a median follow-up of 10 months. The CR, PR, stable disease (SD), progressive disease (PD) of tumor thrombus were 36.6, 39, 17 and 7%, respectively. The 1-year OS was 50.3%, and the median OS was 13 months. Only one patient had an increased bilirubin level.

Wu *et al.*^[20] reported TACE combined with SBRT with 4-8 Gy per fraction for advanced liver cancer with portal/vena cava tumor thrombus. After 4-6 weeks, CR was 8.6%, PR 42.8%, SD 48.6%, and 1-, 2-, 3-year OS were 59.3, 31.6 and 26.6%, respectively, while median survival time was 11 months. Tse *et al.*^[21] recruited 16 cases of primary liver cancer with PVTT, applied an average dose of 36 Gy in 6 fractions, achieved CR of 6%, PR of 19% and SD of 38%. Bujold *et al.*^[22] reported on 56 patients with PVTT who were treated with an average dose of 36 Gy (24-54 Gy in 6 fractions), where the 1- and 2-year OS rates were 44 and 27%, respectively. Multivariate analysis showed that venous tumor thrombus was the worst prognostic factor, HR = 2.47 ($P = 0.01$).

PREOPERATIVE NEOADJUVANT SBRT FOR HCC

Patients with HCC (China liver cancer staging, CNLC IIIa) undergo surgical resection, but only a small part of the patients have long-term survival, and most of the patients have recurrence or metastasis in the short term, leading to death. Radiotherapy alone for PVTT is a palliative therapy. Kamiyama *et al.*^[23] reported on patients with HCC complicated with tumor thrombus who received preoperative neoadjuvant radiotherapy, which was more effective than simple operation. The first branch or main tumor thrombus of portal vein was treated with radiotherapy at 30-36 Gy/10-12 times. After radiotherapy, the thrombus and intrahepatic lesions were removed simultaneously within 2 weeks. Intervention, radiofrequency, anhydrous

alcohol injection and other treatments were given during the follow-up periods. The results showed that the median survival time was 19.6 months for the patients who received surgery combined with external radiotherapy, and 9.1 months for the patients who did not undergo surgery. There was a significant difference between the two groups ($P = 0.036$). The pathology of the surgical specimens showed that 83% of the tumor thrombi were completely necrotic (completely relieved of disease). Therefore, the main purpose of surgery is to improve the control rate of primary HCC and dredge the portal vein. For patients with tumor thrombus, preoperative radiotherapy combined with surgical removal of thrombus is an effective method of comprehensive treatment. A randomized, prospective, multicenter clinical study was conducted in Shanghai Oriental Hepatobiliary Surgery Hospital to compare the survival of patients with HCC and PVTT before operation with or without neoadjuvant radiotherapy^[24]. A total of 82 patients in the radiotherapy group received 18 Gy/6 times of neoadjuvant external radiotherapy; 82 patients in the control group did not receive neoadjuvant radiotherapy. The results showed that the OS rates of radiotherapy group and operation group were 89.0% vs. 81.7%, 75.2% vs. 43.1%, 43.9% vs. 16.7% and 27.4% vs. 9.4% at 6, 12, 18 and 24 months, respectively ($P < 0.001$). The DFS rates of the two groups were 56.9% vs. 42.1%, 33.0% vs. 14.9%, 20.3% vs. 5.0% and 13.3% vs. 3.3% ($P < 0.001$)^[24]. Neoadjuvant radiotherapy can significantly improve the postoperative survival of patients with HCC.

TRANSFORMATION SBRT FOR HCC

Kim *et al.*^[25] of Yonsei University in South Korea reviewed the effect of concurrent radiotherapy and chemotherapy on patients with HCC. A total of 264 patients were selected, most of whom received three-dimensional conformal radiotherapy because of PVTT or residual liver volume insufficiency. Most of them received radiotherapy with a single dose of 1.8 Gy and a total dose of 45 Gy, and 5-fluorouracil (5-FU) was infused in the first and fifth week simultaneous with radiotherapy. One month after radiotherapy, 5-FU and cisplatin were infused once every 4 weeks for 3-12 cycles. Among them, 18 cases were converted into resectable cases. Postoperative pathology showed that 4 cases (22.2%) were completely necrotic and 7 cases (38.9%) were 70%-99% necrotic. Among the 18 patients who underwent surgery, the median survival time and median progression time were 40 and 24 months, respectively, and the median DFS time of the 4 patients with complete tumor necrosis was 54.6 months. Therefore, after conformal radiotherapy, some patients with unresectable HCC could be converted to resectable HCC.

BRIDGING SBRT BEFORE LIVER TRANSPLANTATION

Orthotopic liver transplantation is the most effective treatment for HCC patients with liver transplantation indications. However, due to the limited number of liver donors, many patients may have tumor progression while on the long waiting list, thus losing the best opportunity for liver transplantation. Therefore, bridging therapy to delay tumor progression is very important. SBRT can be used as a bridge treatment for liver cancer patients waiting for liver transplantation. It is neither a new adjuvant radiotherapy nor a transformation radiotherapy. Because SBRT belongs to radical treatment, the majority of HCC patients with T1 or T2 can be reduced to T0. The purpose of liver transplantation is to replace the decompensated liver with normal liver function. The purpose of radiotherapy is to control tumor progression while lacking a liver donor.

Eighteen patients with liver cancer who received SBRT before transplantation were reported by Rochester University Medical Center and William Beaumont Hospital in Michigan^[26,27]. The median dose of radiotherapy was 50 Gy/10 times. There was no serious gastrointestinal adverse reactions or radiation hepatitis. The median waiting period after radiotherapy was 6.3 months. Twelve patients received liver transplantation successfully, and 10 patients showed complete pathological necrosis. The median follow-up period was 19.6 months, and all patients survived. Therefore, SBRT is a safe and effective treatment for liver cancer patients waiting for liver transplantation. It can control the tumor and relieve the pressure of a liver donor before liver transplantation. A study reported^[28] on 379 patients treated with pre-transplantation

bridging therapy, including 36 patients with SBRT, 99 patients with TACE and 244 patients with radiofrequency ablation (RFA). Finally, 312 patients received liver transplantation, 30 in the SBRT group, 79 in the TACE group, and 203 in the RFA group. The 1-, 3- and 5-year survival rates were 83%, 61% and 61% in the SBRT group, 86, 61 and 56% in the TACE group, and 86%, 72% and 61% in the RFA group, respectively ($P = 0.4$). SBRT is as safe and effective as TACE and RFA in the treatment of HCC before transplantation. Compared with TACE and RFA, SBRT has more advantages in the treatment of HCC patients with ascites and prolonged prothrombin time.

POSTOPERATIVE ADJUVANT SBRT FOR HCC

Liver cancer with the distance of less than 1 cm from the bifurcation of the portal vein, the confluence of three main hepatic veins and inferior vena cava, is at high risk of recurrence after liver resection. The 5-year recurrence rate is reported to be more than 90%. At present, there is no effective adjuvant therapy to reduce such a high recurrence rate of this kind of liver cancer. Wang *et al.*^[29] reported the results of radiotherapy for the first time in patients with narrow margin surgery of central type liver cancer, who had retained a silver positioning mark in the operation area guided by postoperative adjuvant radiotherapy.

From 2007 to 2010, 181 patients were analyzed retrospectively. They were divided into three groups: group A: narrow margin surgery combined with postoperative radiotherapy (33 patients), group B: narrow margin surgery (83 patients) and group C: wide margin surgery with cutting edge more than 1 cm (65 patients), and postoperative radiotherapy dose was 46-60 Gy/23-30 times, with a median dose of 56 Gy; the 3-year OS of groups A, B and C was 89.1, 67.7 and 86.0%, respectively, while DFS was 64.2, 52.2 and 60.1%, respectively. Group A had similar OS ($P = 0.957$) and DFS ($P = 0.972$) as group C. Compared with group B, the OS ($P = 0.009$) and DFS ($P = 0.038$) of group A showed significant advantages. The incidence of grade-3 adverse reactions in group A was 12.1% and no more than grade-4 adverse reactions occurred. The study showed that postoperative radiotherapy can make up for the deficiency of narrow margin surgery, and that the effect of narrow margin surgery combined with postoperative radiotherapy can achieve a similar effect as wide margin radical surgery without serious adverse reactions.

Microvascular invasion (MVI) is the most important risk factor for early postoperative recurrence of HCC, which has been proved to be an independent predictor of OS and DFS^[30]. Even for patients with small liver cancer, MVI can increase tumor recurrence rate and significantly reduce OS, and MVI can only be detected by postoperative histological examination.

Wang *et al.*^[31] reviewed and compared the results of conservative therapy (CT), TACE and radiotherapy in 136 HCC patients with MVI. Narrow margin rate in the radiotherapy group was significantly higher than in the other two groups ($P = 0.010$). Postoperative radiotherapy dose was 54-60 Gy/23-30 times, where the results showed that there were significant differences between the radiotherapy group and TACE group and the radiotherapy group and CT group in DFS ($P < 0.05$), and the radiotherapy group and TACE group and the RT group and CT group in OS ($P < 0.05$). Subgroup analysis based on MVI degree and surgical margin showed that RFS and OS of patients in the radiotherapy group with narrow surgical margin were significantly longer than those of the TACE and CT groups, but not related to MVI degree. There was no significant difference in survival outcome between the three groups with wide surgical margin.

SUMMARY

To sum up, surgery is an effective way to cure HCC in the early and middle stages. The high recurrence rate and the lack of effective rescue treatment make the curative effect not very ideal. Although the related research results of surgery combined with SBRT are limited, they all show that it is a safe and effective treatment. As a new way of radiotherapy, preoperative SBRT has shown its unique advantages in the adjuvant

treatment of liver cancer. In a word, it is safe and feasible to combine preoperative and postoperative radiotherapy in the era of multidisciplinary comprehensive treatment, and it has also improved the curative effect. However, more in-depth research is needed to further determine whether it can make HCC patients benefit more from it.

DECLARATIONS

Authors' contributions

Data analysis and interpretation and paper writing: Li JX
Conception and design of the study: Wu H, Zeng Y

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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