

## Radiation therapy has been shown to be adaptable for various stages of hepatocellular carcinoma

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**Received:** April 11, 2014

**Peer-review started:** April 11, 2014

**First decision:** April 28, 2014

**Revised:** May 12, 2014

**Accepted:** June 26, 2014

**Article in press:** June 26, 2014

**Published online:** January 7, 2015

### Abstract

In addition to surgical procedures, radiofrequency ablation is commonly used for the treatment of hepatocellular carcinomas (HCCs) of limited size and number. Transcatheter arterial chemoembolization (TACE), using iodized poppy seed oil, Lipiodol and anticancer drugs, has been actively performed for the treatment of unresectable HCC, particularly in Asian countries. Recently, Sorafenib become available for advanced HCCs when the liver is still sufficiently functional. Sorafenib is an oral multikinase inhibitor with antiproliferative and antiangiogenic effects. However, the effect of sorafenib seems to be inadequate to control the progression of HCC. Radiation therapy (RT)

for HCC has a potential role across all stages of HCC. However, RT is generally not considered an option in HCC consensus documents or national guidelines, primarily because of insufficient supporting evidence. However, the method of RT has much improved because of advances in technology. Moreover, combined treatment of RT plus other treatments (TACE, sorafenib and chemotherapy *etc.*) has become one of the alternative therapies for HCC. Therefore, we should understand the various kinds of RT available for HCC. In this review, we focus on various kinds of external beam radiation therapy.

**Key words:** Hepatocellular carcinoma; Radiofrequency ablation; Transcatheter arterial chemoembolization; Radiation therapy; Sorafenib

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**Core tip:** Radiation therapy (RT) for hepatocellular carcinoma (HCC) has a potential role across all stages of HCC. However, RT is generally not considered an option in HCC consensus documents or national guidelines, primarily because of insufficient supporting evidence. However, the method of RT has much improved because of advances in technology. Therefore, we should understand the various kinds of RT available for HCC. In this review, we focus on various kinds of external beam radiation therapy.

Kondo Y, Kimura O, Shimosegawa T. Radiation therapy has been shown to be adaptable for various stages of hepatocellular carcinoma. *World J Gastroenterol* 2015; 21(1): 94-101 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i1/94.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i1.94>

### INTRODUCTION

Hepatocellular carcinoma (HCC) is the third highest

**Table 1 Transcatheter arterial chemoembolization and radiation therapy *vs* transcatheter arterial chemoembolization**

Ref.	Year	Country	Patient number TACE + RT <i>vs</i> TACE	Child-Pugh (CP-A:CP-B)	Tumor thrombus	Tumor size	Response rate	Over all survival
Koo <i>et al</i> <sup>[22]</sup>	2010	South Korea	42 <i>vs</i> 29	26:16 <i>vs</i> 17:12	All patients had inferior vena cava tumor thrombus	10 ± 4.0 <i>vs</i> 12 ± 3.8 cm	42.9% <i>vs</i> 13.8%	1 yr OS 47.7% <i>vs</i> 17.2%
Zhang <i>et al</i> <sup>[24]</sup>	2009	China	16 <i>vs</i> 29	13:3 <i>vs</i> 19:10	Stenosis: occlusion	< 10 cm : ≥ 10 cm 13:3 <i>vs</i> 21:8	N/A	1 yr OS 32.5% <i>vs</i> 6.9%
Shim <i>et al</i> <sup>[25]</sup>	2005	South Korea	38 <i>vs</i> 35	33:5 <i>vs</i> 32:3	14:2 <i>vs</i> 21:9 yes: no	10.2 <i>vs</i> 9.5cm	65.8% <i>vs</i> N/A	2 yr OS 36.8% <i>vs</i> 14.3%
Zeng <i>et al</i> <sup>[20]</sup>	2004	China	54 <i>vs</i> 149		12:26 <i>vs</i> 10:25 Non		76% <i>vs</i> 31%	1 yr OS 71.5% <i>vs</i> 59.6%

TACE: Transcatheter arterial chemoembolization; RT: Radiation therapy; OS: Overall survival.

cause of cancer-related death worldwide<sup>[1]</sup>. Risk factors for the incidence of HCC include hepatitis B, hepatitis C, alcoholic hepatitis, non- alcoholic fatty liver disease (NAFLD), and liver cirrhosis from any cause. Among these causes, chronic infection of hepatitis B or hepatitis C virus (HBV/HCV) can strongly affect the incidence of HCC<sup>[2]</sup>. Therefore, the age of HCC patients might be affected by the cause of HCC. The average age of HCC patients in Japan is higher than that in other Asian-Pacific regions due to the incidence of HCV-related HCC<sup>[3]</sup>. In Asia and Africa, approximately 80% of cases of HCC are due to infection with HBV<sup>[4]</sup>. There are relatively many HCV-related HCC patients in South America (particularly Brazil)<sup>[5]</sup>.

HCC tends to remain within the liver, although multifocality and vascular invasion are common<sup>[6]</sup>. A balance between the remaining liver function and tumor factors influences the selection of various kinds HCC treatment<sup>[7]</sup>. Surgical resection of HCC, an option for a limited number of HCCs, results in 5-year survival rates of 60%-70%<sup>[8]</sup>. Liver transplantation (LT) can cure both the HCC and underlying liver disease. A meta-analysis suggested that LT provides increased survival and lower recurrence rates than surgical resection for HCC patients<sup>[9]</sup>. In addition to surgical procedures, radiofrequency ablation (RFA) is commonly used for the treatment of HCCs of limited size and number<sup>[8]</sup>. Transcatheter arterial chemoembolization (TACE), using iodized poppy seed oil, Lipiodol and anticancer drugs, has been actively performed for the treatment of unresectable HCC, particularly in Asian countries<sup>[10]</sup>. However, HCCs remain viable in and around the tumor-capsule, which is supplied by both arterial and portal blood, and these cells are often responsible for late recurrence after TACE treatment<sup>[11]</sup>. Recently, Sorafenib become available for advanced HCCs with sufficient remaining liver function<sup>[12]</sup>. Sorafenib is an oral multikinase inhibitor with antiproliferative and antiangiogenic effects. It has been shown to inhibit the activity of serine/threonine kinase c-Raf (Raf-1) and B-Raf; the mitogen-activated protein kinases MEK and ERK; vascular endothelial growth factor receptors (VEGFR)-1, 2, and 3; platelet-derived growth factor receptors (PDGFR)- $\alpha$  and  $\beta$ ; cytokine receptor c-KIT; the receptor tyrosine kinases

Flt-3 and RET; and the Janus kinase/signal transducer and activator of transcription pathway. The intracellular signaling pathway Raf/MEK/ERK and the extracellular receptors VEGFR and PDGFR should be inhibited by sorafenib<sup>[13]</sup>. However, the effect of sorafenib seems to be inadequate to control the progression of HCC. In addition to sorafenib, hepatic arterial infusion chemotherapy (HAIC) has been used for advanced HCC<sup>[14]</sup>.

Radiation therapy (RT) for HCC has a potential role across all stages of HCC. However, RT is generally not considered an option in HCC consensus documents or national guidelines, primarily because of insufficient supporting evidence<sup>[15,16]</sup>. However, methods of RT have greatly improved because of advances in technology. Moreover, combined treatment of RT plus other treatments (TACE, sorafenib and chemotherapy *etc.*) has become one of the alternative therapies for HCC. Therefore, we should understand the various kinds of RT available for treating HCC. In this review, we focused on various kinds of external beam radiation therapy.

## COMBINED TREATMENT

Many groups reported that RT combined with locoregional therapy such as TACE could be effective for the control of HCC (Table 1). Several general approaches with such combinations are used<sup>[17-21]</sup>. One of them, RT specifically targeting the tumor thrombus, can be used before TACE<sup>[17,22]</sup>. In 1989, Takagi *et al*<sup>[23]</sup> reported a 29% response rate in 7 patients irradiated for HCC with portal venous thrombosis. A group of 42 patients treated only for tumor thrombosis were compared with control patients treated with TACE without RT. RT combined with TACE had higher response rates (43% *vs* 14%) and overall survival (medial, 11.7 mo *vs* 4.7 mo)<sup>[22]</sup>. In another comparative study, significantly improved survival was reported in 16 patients treated with RT combined with TACE compared with 29 patients treated with TACE alone (33% *vs* 7% 1-year survival)<sup>[24]</sup>. Since RT could be effective for the treatment of tumor thrombus, RT combined with TACE should be used for the treatment of HCC with tumor thrombus.

As another approach, RT could be used as a consolidative treatment after TACE. A systematic review of 17 trials

found that patients treated with RT combined with TACE had improved survival compared to patients treated with TACE alone. Moreover, serious adverse events were not increased, with the exception of an elevation of the total bilirubin level. Another group reported the use of local radiotherapy as a complement to incomplete transcatheter arterial chemoembolization in locally advanced hepatocellular carcinoma<sup>[25]</sup>. In 73 patients treated with incomplete TACE, TACE was repeatedly performed in 35 patients, and the remaining 38 patients were also treated with local RT. The 2-year survival rate was significantly higher in the RT combined with TACE group than in the TACE alone group (36.8% *vs* 14.3%,  $P = 0.001$ )<sup>[25]</sup>. Another group reported the efficacy of 3-dimensional conformal RT for patients with unresectable HCC after incomplete TACE. The overall survival rate was 72.0% at 1 year and 45.6% at 2 years<sup>[26]</sup>. In addition to a comparison between RT combined with TACE and TACE only alone, the feasibility of RT combined with TACE in comparison with sorafenib for advanced HCC has been investigated. The overall survival of the RT combined with TACE group was longer compared to the sorafenib treatment in locally advanced HCC patients without distant metastasis<sup>[27]</sup>. Moreover, another group reported a comparison between surgical resection and conformal RT combined with TACE for resectable HCC with portal vein tumor thrombus. In this report, conformal RT combined with TACE yielded better survival than surgical resection for HCC with portal vein thrombosis<sup>[28]</sup>.

In addition to RT combined with TACE, a combination therapy of RT and sorafenib has been considered, recently<sup>[29-31]</sup>. Yu *et al.*<sup>[31]</sup> reported that sorafenib enhanced the radiosensitivity of human HCC cell lines in a schedule-dependent manner. Sorafenib induced DNA damage and suppressed the DNA repair capacity, decreased radiation-activated NF-kappaB and increased the radiation-induced apoptosis. Moreover, RT combined with sorafenib was carried out in 31 patients<sup>[29]</sup>. The median overall survival was 7.8 mo (95%CI: 3.0-12.6)<sup>[29]</sup>. The combined treatment of sorafenib and RT was feasible and induced substantial tumor responses in the target lesions.

The efficacy of RT combined with HAIC was reported by several groups<sup>[32,33]</sup>. A group investigated the efficacy of HAIC using 5-FU and systemic interferon (IFN)-alpha for advanced HCC with venous tumor thrombosis (VTT) in the hepatic vein trunk (Vv2) or inferior vena cava (Vv3)<sup>[32]</sup>. HAIC-5-FU/IFN, despite being ineffective, could be useful in combination with radiotherapy for VTT to improve the prognosis. Another group evaluated the efficacy of intra-arterial 5-FU and subcutaneous interferon combined with image-guided RT in advanced HCC with PVTT. The overall median survival was significantly longer in the combination group (12.0 mo, 95%CI: 9.3-17.6 mo) than in the non-combination group (9.1 mo, 95%CI: 5.5-11.1 mo) ( $P = 0.041$ )<sup>[33]</sup>.

## STEREOTACTIC BODY RADIOTHERAPY

With the progress of radiation therapy, it was found to be

effective for HCC<sup>[34]</sup>. It provides a better curative effect by irradiating the tumor more precisely and reducing damage of the normal part of the liver. Therefore, recently, stereotactic body radiotherapy (SBRT) has become widely used because of its stronger curative effect. SBRT was used to treat intracranial targets from the 1950s<sup>[35,36]</sup>. In recent years, progress in the fields of image-guided radiotherapy and computer science has enabled its use for extracranial targets<sup>[36]</sup>. SBRT for HCC was made possible by establishing a method for tracing the regions of the body that fluctuate with the respiratory movement<sup>[37]</sup>. SBRT is suitable for non-resectable small HCCs as a noninvasive treatment. Although RFA treatment is very effective, it can sometimes be problematic because the puncture route taken could result in damage to nearby organs. In addition, if blood vessels exist near the HCC, the blood flow can reduce the thermal effects of RFA<sup>[38]</sup>. Therefore, medical devices used for laparoscopy or artificial hydrothorax can be used to perform RFA. However, technical skill is required to treat HCC properly. SBRT is now considered as alternative to RFA. Recent studies indicate that the results of RFA are equal to those of surgery<sup>[39,40]</sup>. There are few articles that compared the surgery with SBRT directly. On the other hand, SBRT is not described in the Barcelona Clinic Liver Cancer system<sup>[41]</sup> nor in the algorithm created by the Japan Society of Hepatology<sup>[15]</sup>. However, in recent years many good results have been reported for SBRT. The curative effects and side effects of SBRT should be the focus of discussions about its suitability as an alternative to RFA. The articles concerning SBRT reviewed here had different protocols. There are many reports about the effectiveness and safety of SBRT (Table 2). Generally, SBRT is considered for lesions smaller than 5 cm in diameter. The treatment dose range was 6-15 Gy per day and the total dose was 18-50 Gy in 1 to 10 fractions<sup>[36,42-51]</sup>. The daily irradiation dose is very high, so appropriate planning at the irradiation center is required.

SBRT is effective for HCC, with especially a 1 year local control rate of more than 90%<sup>[36,43,48,50]</sup>. However, the complete response rate was 20%-60%<sup>[43,44,47]</sup>, lower than that of RFA. SBRT cannot completely replace RFA. However, it is reported that the complete response rate is higher for smaller HCCs. Kwon *et al.*<sup>[47]</sup> described that the progression-free survival rate changes at 32 cc of tumor volume.

Although it has been described that SBRT did not produce major side effects. The side effects of SBRT include acute toxicities and late toxicities. Acute toxicities are elevations in liver enzymes, thrombocytopenia, leukopenia and nausea. Many of these are grade 1 to grade 3<sup>[43,44,52]</sup>. Late toxicities occur in the first six months and are rare. Late toxicities include decompensation and duodenal ulcer. A few patients have died of liver failure by SBRT<sup>[47,48]</sup>. If the patient's original liver function can be classified as Child-PughB, caution is required. SBRT is a concentrated irradiation treatment, but it may be lethal when employed at unsuitable hepatic lesions in patients with poor liver function. Concerning the liver

**Table 2 Stereotactic body radiation therapy in hepatocellular carcinoma**

Ref.	Patient number	Tumor	Back ground	Median tumor volume	Median dose (Gy)	Fraction	Follow up (mo)	Local control	Overall survival	Adverse effect Acute toxicity grade $\geq 3$ Late toxicity grade $\geq 3$
Andolino <i>et al</i> <sup>[42]</sup>	60	HCC	LC (CP-A: 36, CP-B: 24)	3.2 cm	44	3	27	2 yr local control 90%	2 yr OS 67%	0% N/A
Choi <i>et al</i> <sup>[44]</sup>	20	HCC	LC (CP-A: 15, CP-B: 5), PVT: 4	2-6.5 (3.8 cm)	50	5-10	3-55 -23		1 yr OS 70% 2 yr sOS 43.1%	0% N/A
Goodman <i>et al</i> <sup>[45]</sup>	26	meta CCC HCC	meta: 19, CCC: 5, HCC: 4	0.8-146.6 (32.6 cc)	22.5-46.6 -34.8	1	2-55 -17		1 yr OS 64.3% 2 yr OS 50.4%	0% N/A
Huang <i>et al</i> <sup>[46]</sup>	36	HCC	LC (CP-A: 28, CP-B: 7, CP-C: 1)	1.1-12.3 (4.4 cm)	25-48 -37	4-5	14	1 yr in-field failure free rate 87.6% 2 yr in-field failure free rate 75.1%	2 yr OS 72.6%	2.8% (1: gastric ulcer) N/A
Kwon <i>et al</i> <sup>[47]</sup>	42	HCC	LC (CP-A: 38, CP-B: 4, CP-C: 0)	15.4-81.8 (15.4 cc)	30-39	3	8.4-49.1 -28.7	1 yr in-field progression-free survival rate 72.0% 3 yr in-field progression-free survival rate 68.0%	1 yr OS 72% 3 yr OS 67.5%	0% 1% (1: liver failure)
Louis <i>et al</i> <sup>[36]</sup>	25	HCC	LC (CP-A: 22, CP-B: 3)	1.8-10.0 (4.5 cm)	45	3	1-24 -12.7	1 yr local control rate 95%	1 yr OS 79% 2 yr OS 52%	4% (1: hepatic/epigastric pain) 10% (1: gastro duodenal ulcer, 1: hepatic toxicity)
Méndez Romero <i>et al</i> <sup>[48]</sup>	25	meta HCC	meta: 17, HCC: 8	0.5-7.2 (3.2 cm)	25-37.5	3-5	0.5-31 -12.9	1 yr local control rate 94% 2 yr local control rate 82%	1 yr OS 82% 2 yr OS 54%	16% (1: patient died in a hepatic toxicity and bleeding from varices. 3: hepatic toxicity.)
Takeda <i>et al</i> <sup>[50]</sup>	16	HCC	LC (CP-A: 14, CP-B: 2)	3.4-72 (13.6 cm <sup>3</sup> )	35-50	5-7 (6)	8.1-33.1 -20.4	1 yr local control rate 90% <	All patients were alive	0% 0% 0%
Tse <i>et al</i> <sup>[51]</sup>	41	HCC CCC	HCC (CP-A: 31), CCC (10)	9-1913 (173 mL)	24-54 -36	6	10.8-39.2 (17.6)	1 yr in-field local control rate 65%	1 yr OS 51%	43% (13: hepatic toxicity, 1: hemato toxicity, 1: lethargy, 3 : nausea) 6% (1: GI bleeding, 1: bowel obstruction)

HCC: Hepatocellular carcinoma; LC: Local control; CP: Child-Pugh.



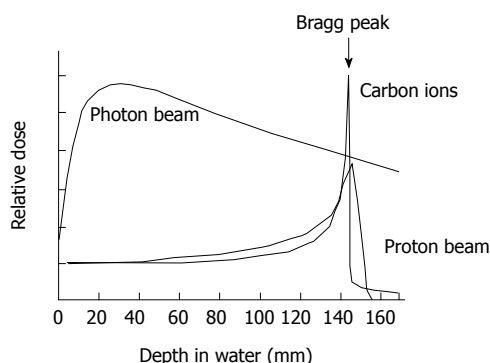


Figure 1 Particle beam therapy.

function, it is reported that the CP value generally rises after the treatment. Takeda *et al*<sup>[50]</sup> reported that patients with sufficient liver function don't experience any major problems and show improved liver function at one year after SBRT.

SBRT has few side effects and good disease control potency. In order to enhance the therapeutic effect, SBRT after TACE has been performed<sup>[35,36,44,46,48,50]</sup>. The combination of RT and TACE has been shown to be more effective only when compared to RT alone<sup>[38]</sup>. SBRT is a very effective therapy and has the possibility of expanded use with further technological improvements.

## PARTICLE BEAM THERAPY

Clinically, proton beam and heavy iron therapies are described as particle beam therapies<sup>[53]</sup>. Heavy ion therapy uses a carbon ion beam. The particle beam therapy is produced by irradiating carbon nuclei or high energy protons using a cyclotron accelerator or synchrotron accelerator<sup>[54]</sup>. It requires a relatively large facility because the accelerator itself is quite huge. Therefore, facilities for particle beam therapy are limited in number and its use is limited clinical trials. In general, X-rays are reduced gradually in the human body. On the other hand, an accelerated particle beam emits maximum energy just before it is stopped. It makes a peak of steep energy called the Bragg-Peak<sup>[55]</sup> (Figure 1). Therefore, particle beam therapy creates maximum energy at the depth of a lesion.

Using particle beams for clinical applications was first proposed by Wilson in 1946<sup>[56]</sup>. In the early 1950, proton and helium ion beams were studied at Lawrence Berkeley National Laboratory (LBNL) in the United State<sup>[57]</sup>. LBNL paved the way for heavy ion therapy in the 1970's. In 1994, the first Phase I and II heavy ion treatment took place at Heavy Ion Medical Accelerator in Chiba, Japan. Twenty-four HCC patients in Phase I and II were treated with total doses ranging from 49.5 GyE to 79.5 GyE given in 15 fixed fractions and 5 wk<sup>[58]</sup>. No severe side effects appeared and the overall tumor response rate was 71%. The local control and overall survival rate was 92% and 92%, 81% and 50%, and 81% and 25% at 1, 3, and 5 years. The heavy ion beam is similar to normal

radiation therapy but it can expect to have a strong effect for deep lesions. Heavy ion beam therapy was effective for HCC in the porta hepatis<sup>[59]</sup>. This report showed that the 5-year overall survival, local control rate, and toxicities were not significantly different between the porta hepatis and control groups.

Carbon ion beams have the advantage of a higher cytotoxic effect than proton beams. Proton beams can be irradiated from any direction, and they can also be applied for cases in which other treatments are not suitable. Proton beam therapy yielded good results when the dose of radioactivity and the cautery range for the lesion in contact with the gastrointestinal tract and a porta hepatis region were properly regulated<sup>[60-62]</sup>.

Particle beam therapy is an effective treatment that can overcome some of the normal radiation therapy. It is a major disadvantage that treatment facilities are limited. Further clinical applications are expected in the future since such facilities have been increasing.

## EXTRAHEPATIC METASTASES

Intrahepatic lesions of HCC are controlled by treatment surgery, RFA, TACE and RT. Sometimes, lesions in the liver can be controlled, but extrahepatic lesions develop. In HCCs, intrahepatic lesions more strongly affect the prognosis compared with extrahepatic lesions. In a report by Uchino *et al*<sup>[63]</sup>, extrahepatic metastases were related directly to death in 23 patients (7.6%) of 342 patients. Seventeen patients died from respiratory failure due to pulmonic metastasis, five patients from brain hemorrhages due to cerebral metastasis, and one patient from hemorrhages due to fractures from bone metastasis. Bone metastasis has little influence as a direct cause of death. However, bone fractures due to bone metastasis reduce the performance status, and treatment is important to prevent a decrease in quality of life. Habermehl *et al*<sup>[64]</sup> reported that the response rate to palliative radiotherapy for bone metastasis from CCC (11 patients, 19 lesions) and HCC (30 patients, 48 lesions) was 77%. It did not contribute to the overall survival for advanced cancer, but such radiation therapy contributed to the amelioration of pain (63 lesion, 94%), neurologic complications (9 lesions, 13%) and unstable lesions with a risk of pathologic fracture (6 lesions, 9%). In addition, Jiang *et al*<sup>[65]</sup> carried out palliative irradiation for lung metastases with symptoms (stuffy chest, hematosputum and cough). In 92.3% of the patients, significant symptoms were completely or partially relieved. Other groups reported the effect of RT on lymph node metastasis<sup>[66]</sup> and adrenal gland metastasis<sup>[67]</sup>. The curative effect of RT for distant metastasis of HCC is sufficiently meaningful. In the future, the primary tumor will be controlled, and RT should provide useful treatment oligometastases<sup>[68]</sup> and local recurrences.

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P- Reviewer: Niibe Y, Storto G

S- Editor: Ma YJ L- Editor: A E- Editor: Liu XM







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ISSN 1007-9327

