Controversies in Radiotherapy for Hepatocellular Carcinoma

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Abstract

Radiation therapy for liver carcinomas has been used in some hospitals in North America and Europe, but widely in Asia. However, the role of radiation therapy in the management of liver carcinoma has not been recognized in liver cancer society, especially in North America and Europe. The modern radiation techniques, 3-dimensional radiation therapy, intensity-modulated radiation therapy, stereotactic body radiotherapy, and proton and carbon ion beam radiation therapy have yielded very encouraging outcome. Recently, the role of radiation therapy just started to be recognized by NCCN guideline.

In the radiation therapy society, there were controversies regarding the radiation techniques: (1) What was the optimal management to control target motion, especially for beam scanning delivery in proton and carbon ion therapy? (2) What were the optimal radiation fractionation and total dose for hypofractionated or stereotactic body radiation therapy? (3) What were the normal liver tolerances for the livers with different degrees of hepatic cirrhosis, when different irradiation fractionations and total doses were applied? (4) What were the appropriate indications for different radiation techniques?

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1 Introduction

Liver cancer is one of the leading cancer-related deaths globally. The incidence and mortality of liver cancer, respectively, ranked the sixth and the fourth places in the world. The estimated number of new liver cancer patients is 841,080, and the death is 781,631 patients in 2018 (Bray et al. 2018). In China the liver cancer incidence ranked the fourth place in cancer incidence and the third place in mortality according to the recent epidemiological investigation (Chen et al. 2016). Among liver cancers hepatocellular carcinoma (HCC) accounts for 85%, which results from hepatitis B or C virus-induced hepatic cirrhosis. Although HCC could be detected at early stages by alpha fetal protein (AFP), 60–70% of HCC is diagnosed at late stages in China.

The standard care of liver cancers is surgery, but only around 25% of liver cancer cases are candidates for surgery when diagnosed. The majority of liver cancers are either technically unresectable due to the locally advanced or medically inoperable due to poor hepatic functions, comorbidity, or contraindications for anesthesia. Therefore other alternative modalities play important roles in the management of liver cancers. However, for early stages of HCC, even after surgery the survivals are not satisfactory with 5-year survivals from 60% to 70%.

Currently, it has gradually been recognized the role of radiotherapy (RT) in the management of liver cancers since 1990s, when the modern RT technique of 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) was used in clinical RT practice. In the past two decades the clinical experience in RT for liver cancers has been accumulated, but not in a mature stage. There are controversies in the application of RT for liver cancers, and much room needs to be explored.

This chapter is mainly focusing on HCC and discusses the controversies based on BCLC stage proposed by Barcelona-Clinic Liver Cancer Group in 1999.

2 The Role of RT in the Management of HCC

2.1 BCLC Stage 0 and Stage A

BCLC stage 0 is the very early stage with single nodule of <2 cm in diameter, or carcinoma in situ, and with hepatic function of Child-Pugh A and performance status (PS) 0; and BCLC stage A is early stage with single or 3 nodules of ≤3 cm and Child-Pugh A-B and PS 0.

The flowchart of BCLC/American Association for Study of Liver Disease (AASLD) has been widely used in the world (Santambrogio et al. 2013; Kim et al. 2011). In this flowchart, for the early stages, surgical resection, liver transplantation, or percutaneous ethanol injection (PEI)/radiofrequency ablation (RFA) was the recommended the standard care. There was even no mention for the role of RT in the management of early stages of HCC. As the same as in AASLD flowchart, there was no role for RT in the guidelines of EORTC (Management of hepatocellular carcinoma, European Association for the Study of the Liver 2012) and ESMO–ESDO. However, there was a short remark about external RT, but the level of evidence and the grade of recommendation of 3C, which had the poorest evidence and the weakest recommendation. However, the role of internal RT was above the external RT with 2B of evidence level and recommendation grade (Verslype et al. 2012). Although those flowcharts were proposed to be further improved (Livraghi et al. 2010), EORTC stated it clear that "the benefits of external three-dimensional conformal radiotherapy have only been tested in uncontrolled investigations. There is no scientific evidence to recommend these therapies as primary treatments of HCC and further research testing modern approaches is encouraged."

NCCN guideline has been widely used globally. In 2017 NCCN guideline of HCC for BCLC stage 0 and A (T1N0M0) (www.nccn.org), the treatment of choice was surgery or liver

transplantation. For patients of BCLC stage 0 and A, who are not fit for surgery or ineligible for liver transplantation, the treatments recommended are locoregional therapy, which includes ablation by RFA, PEI, arterially directed therapies [trans-artery chemoembolization (TACE) and radioembolization (RE)], and external beam radiation therapy (EBRT) (conformal or stereotactic). Although EBRT has been listed as one of the options for locoregional therapies, the evidence is listed as the category 2B, which means lower level evidence. In contrast, ablation and arterially directed therapy were listed as the evidence of category 2, which means the uniform NCCN consensus. In other words, RT was not the uniform consensus in NCCN panel members, and the role of RT was inferior to ablation and arterial therapy. Nevertheless, it was changed that RT was proposed as one of the treatment choices for BCLC 0-1 with the evidence of 2A in 2018 NCCN guideline. It implies that liver cancer society in North America started to recognize the role of RT in the management of HCC.

Of course, for BCLC stage 0 and A, the surgical resection is believed to be the only modality to cure HCC, and yields the best survivals among all the treatments available so far. However, the candidates for surgery are limited by surgical contraindications due to the cardiovascular comorbidities, poor hepatic function, or patient refusal. For liver transplantation, it is a promising choice for HCC as it could eradicate HCC and its essential cause, cirrhotic liver, but because of shortage of the donor it could not be widely used. However, BCLC flowchart did not define what the treatment choice was for them.

In Chinese guideline for HCC external RT with 3D-CRT and IMRT was recommended for those with early stages of HCC, who were not suitable to surgery (Chinese Ministry of Health 2011; Chinese Society of Clinical Oncology 2018). The significantly different attitude to RT in China, and also in Asia, was due to that a large population of HCC had been treated by RT, and the outcome was encouraging.

In spite of not being recognized by the liver society in North America and Europe 3D-CRT and IMRT, and lately most advanced RT techniques, like stereotactic body radiotherapy (SBRT), stereotactic ablative body radiotherapy (SABR), and proton and heavy ion RT, have been gradually used in Asia since 1990. At the early time only locally advanced HCC was irradiated, and gradually for early-stage HCC. The outcomes were very encouraging.

2.1.1 3D-CRT/IMRT

3D-CRT/IMRT was innovated in 1990, which could deliver high dose to tumor and meantime spare adjacent organs at risk (OAR). Since then this technique has been used to treat HCC, mainly for those HCC unfit to surgery. In early 2000, conventional fractionation with 2 Gy per fraction and total doses from 30 Gy to 60 Gy were applied for 3D-CRT/IMRT alone, or combined with TACE. The outcomes were very good with the median survival time (MST) of 10–25 months, and 1-year overall survival (OS) of 47–93% and 3-year OS of 22–35% (Table 1).

2.1.2 SBRT/SABR

SBRT/SART was invented over a decade ago. The mechanism of SBRT/SABR is multiple X-ray beams focused at the center of tumor and delivered at very high doses to tumor while low dose, but large volume, to the normal organs adjacent to it.

Princes Margaret Hospital reported 102 patients treated by SBRT of 24–54 Gy in six fractions. All patients had Child-Pugh A disease and >700 mL of non-HCC liver. The associated liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol related in 25%, others in 14%, and none in 7%. TNM stage was stage III in 66%, and 61% had multiple lesions. The median gross tumor volume was 117 mL. Tumor vascular thrombosis (TVT) was present in 55%, and extrahepatic disease was present in 12%. Toxicity of ≥grade 3 was seen in 30% of patients. Local control rate at 1 year was 87%. Seven patients (two

Table 1 Outcome of 3D-CRT/IMRT by conventional fractionation irradiation in hepatocellular carcinoma

Study	Patient No.	Treatment	Dose (Gy)	MST (mo)	OS
Seong (1999)	30	3D-CRT + TACE	44 (2 Gy/fx)	17	3-year 22.2%
Seong (2000)	27	3D-CRT	40–60 (2 Gy/fx)	14	3-year 21.4%
Park (2002)	158	3D-CRT	40–60 (1.8 Gy/fx)	10	2-year 19.9%
Liu (2004)	44	3D-CRT	39.6–60 (1.8 Gy/fx)	15.2	1-year 60% 3-year 32%
Seong (2003)	158	3D-CRT + TACE	25.2–50.0 (1.8 Gy/fx)	16	1-year 59% 5-year 9%
Guo (2003)	76	3D-CRT + TACE	30–50 (1.8–2.0 Gy/fx)	19	1-year 64% 5-year 19%
Zeng (2004)	54	3D-CRT + TACE	36–60 (2 Gy/fx)	20	1-year 72% 3-year 24%
Park (2005)	59	3D-CRT	30–55 (2–3 Gy/fx)	10	1-year 47% 2-year 27%
Zhou (2007)	50	3D-CRT + TACE	30–54 (2 Gy/fx)	17	3-year 26%
Hsu (2006)	121	3D-CRT	45–75 (1.5 Gy/fx, 2 fx/d)	19	2-year 44.6%
Kim (2006)	70	3D-CRT	44–54 (2–3 Gy/fx)	18	2-year 17.6%
Mornex (2006)	27	3D-CRT	66 (2 Gy/fx)	NA	NA
Ren (2011)	40	3D-CRT + TACE	42–62 (2 Gy/fx)	–	LC 2-year 93% OS 2-year 62%

3D-CRT 3-dimensional conformal radiation therapy, *d* day, *fx* fraction, *IMRT* intensity-modulated radiation therapy, *LC* local control, *mo* month, *MST* median survival time, *OS* overall survival, *TACE* trans-catheter artery chemotherapy and embolization, *wk* week, *yr* year

with TVT) died possibly related to treatment 1.1–7.7 months after SBRT. Median OS was 17.0 months. Authors thought that their results provided strong rationale for a randomized trial to test the role of SBRT in HCC (Bujold et al. 2013).

Kang reported 50 inoperable HCC of a greatest tumor dimension of 2.9 cm (1.3–7.8 cm), and incomplete response after TACE. Moreover, five patients had portal vein tumor thrombosis (PVTT). SBRT was used with the doses from 42 Gy to 60 Gy in three fractions (median, 57 Gy). The 2-year LC rate was 94.6%; OS 68.7%; and PFS 33.8%. Three patients (6.4%) experienced grade 3 gastrointestinal toxicity, and two patients (4.3%) grade 4 gastric ulcer perforation (Kang et al. 2012).

Sixty-three untreated solitary HCC patients were irradiated by SABR with doses of 35–40 Gy in five fractions in Takeda's report. Twenty patients were treated with only SABR, and 43 patients with SABR after TACE. The 1-year, 2-year, and 3-year LC rates were 100%, 95%, and 92%; the intrahepatic recurrence-free rates were 76%, 55%, and 36%; and the OS were 100%, 87%, and 73%, respectively. The acute, subacute, and chronic phases of ≥grade 3 were observed in 10, 9, and 13 patients, respectively. Authors concluded that SABR was safe and an alternative for HCC unfit for surgery or ablation (Takeda et al. 2014).

Sanuki reported a retrospective study on HCC treated by SBRT for the curative intent. HCC with a single (either solitary or recurrent) lesion; unfeasible, difficult, or refusal to surgery or percutaneous ablative therapies; Child-Pugh A or B; and tumors ≤5 cm were selected for the analysis. A total of 185 patients were collected (48 in 35 Gy group, and 137 in 40 Gy group). The 3-year LC and OS were 91% and 70%, respectively. Acute toxicities of ≥grade 3 were observed in 24 cases (13.0%), and 19 cases (10.3%). Grade 5 of liver failure occurred in two patients in the 35 Gy group (Sanuki et al. 2014).

Table 2 summarizes the outcome of early stage of liver cancers, mainly HCC treated by SBRT/SABR published since 2000. The fraction size was from 4 Gy to around 10 Gy. The LC ranged from 66% to 75% at 2 years, and 21% to 75% at 2 years and 59% to 73% at 3 years,

Table 2 Outcome of liver cancers treated by hypofractionated RT or SBRT/SARB

	No. of pts	Tumor size	Dose	LC	OS
Wu (2004)	94	10.7 cm	48–60 Gy (4–8 Gy/fx)	93% (1 year)	26% (3 years)
Liang (2005)	128	459 cm^3	40–60 Gy (4–8 Gy/fx)	–	33% (3 years)
Choi (2008)	31	25 mL	30–39 Gy/3 fx	95% (1 year)	52% (2 years)
Kwon (2010)	42	15 mL	30–39 Gy/3 fx	68% (3 years)	59% (3 years)
Seo (2010)	38	41 mL	33–57 Gy/3–4 fx	66% (2 years)	61% (2 years)
Andolino (2011)	60	3.2 cm	CP-A 44 Gy/3 fx CP-B 40 Gy/5 fx	90% (2 years)	67% (2 years)
Kang (2012)	50	2.9 cm	42–60/3 fx	94.6% (2 years)	68.7% (2 years)
Huang (2012)	36	4.4 cm	25–48 Gy/4–5 fx	75% (2 years)	64% (2 years)
Dewas (2012)	153	3.3 cm	45 Gy/3 fx	84% (1 year)	75% (2 years)
Ibarra (2012)	32	HCC 334 mL CCC 80 mL	HCC 18–26 Gy/10 fx ICC 22–30 Gy/15 fx	75% (2 years)	55% (2 years)
Bujold (2013)	102	7.2 cm	24–54 Gy/16 fx	87% (1 year)	MST 17 months
Bae (2013)	35	131 mL	30–60 Gy/3–5 fx	51% (3 years)	21% (2 years)
Takeda (2014)	63		35–40 Gy/5 fx	92% (3 years)	73% (3 years)
Sanuki (2014)	185	8 mL	CP-A 40 Gy/5 fx CP-B 35 Gy/5 fx	91% (3 years)	70% (3 years)
Lazarev (2018)	53	Central	BED10 = 72 Gy	87.9% (2 years)	39% (2 years)

CP-A Child-Pugh A, *CP-B* Child-Pugh B, *fx* fraction, *HCC* hepatocellular carcinoma, *ICC* intrahepatic cholangiocellular carcinoma, *LC* local control rate, *OS* overall survival rate, SABR stereotactic ablative body radiotherapy, *SBRT* stereotactic body radiotherapy

respectively. The advantages of RT over PEI and RF include the following: (1) Up to 5 cm diameter lesion could be effectively controlled by RT. (2) Lesions located adjacent to large vessels and biliary ducts are not contraindications. (3) RT is totally noninvasive. The SBRT/SARB data were mainly from retrospective studies, and the follow-up time was not long enough, but the benefit from SBRT/SARB is significant.

2.1.3 Proton and Heavy Ion RT

In the past two decades, particle ion RT, predominantly proton and carbon ion, has been adopted in treating HCC. Particle ion RT is the latest innovation in RT technology, the cutting-edge technique. Because of the physical characteristic of Bragg peak dose distribution very high RT doses could be delivered to tumors, and meantime spare the adjacent normal organs significantly. Moreover, the carbon ion, as high linear energy transfer (LET) beam, facilitates with high biological effect, which could effectively kill those photon-resistant tumor cells, like hypoxic cells in HCC. Thus, particle ion RT has great potential to cure HCC.

Chiba in Tsukuba University, Japan, first reported the outcome of 162 patients with HCC (192 lesions) treated by proton beam RT from 1985 to 1998. All patients were medically inoperable or technically unresectable due to hepatic dysfunction, multiple tumors, and recurrence after surgical resection, or concomitant illnesses. The median diameter of tumor was 3.8 cm (1.5–14.5 cm). Twenty-five out of 162 patients had portal vein tumor thrombosis (PVTT). The hepatic background was Child-Pugh A of 82 cases (50.6%), Child-Pugh B of 62 cases (38.3%), and Child-Pugh C of 10 cases (6.2%). The median total dose of proton irradiation was 72 GyE (Gy equivalent to ^{60}Co) in 16 fractions over 29 days. The fraction sizes were from 4.5 GyE to 5 GyE and the total doses from 50 GyE to 72 GyE. The local control rate at 5 years was 86.9% for 192 tumors among the 162 patients. The 5-year OS was 23.5%. The late toxicity of ≥G2 occurred in 3% of patients. This was the first paper in the literature to show that proton beam RT was effective in treating HCC, and demonstrated that it's safe and well tolerable. They also proposed that proton RT was a useful

treatment for either cure or palliation for HCC, irrespective of tumor size, tumor location, presence of vascular invasion, impaired hepatic functions, or coexisting intercurrent diseases (Chiba et al. 2005).

Tsukuba University continued proton RT. From 2001 to 2007, they treated a total of 318 HCC. There were 234 patients (73.6%) of Child-Pugh A, 77 (24.2%) of Child-Pugh B, 7 (2.2%) of Child-Pugh C, 150 (47.2%) of T1, 107 (33.6%) of T2, and 61 (19.2%) of T3. A total dose of 77 GyE in 35 fractions was used for tumors within 2 cm of the digestive organ, 72.6 GyE in 22 fractions was used for tumors within 2 cm of the porta hepatis, and 66 GyE in 10 fractions was delivered to peripheral tumors >2 cm from both the gastrointestinal tract and the porta hepatis. OS rates for all 318 patients were 89.5%, 64.7%, and 44.6% at 1 year, 3 years, and 5 years, respectively. Five-year LC rate was 83.3%. No treatment-related death was observed. No patients discontinued the treatment because of liver toxicity. Only four patients developed radiation-related gastrointestinal toxicities (three with grade 2 GI ulcers and one with grade 3 hemorrhage of the colon, all of which were successfully treated by surgery) (Nakayama et al. 2009).

National Cancer Center in Japan treated 30 old patients with HCC (median age of 70 years) with median diameter of 45 mm (25–82). Twenty patients were associated with Child-Pugh A, and ten patients class B. Proton of 76 GyE in 20 fractions and 5 weeks was delivered. After a median follow-up period of 31 months, only one patient experienced recurrence of the primary tumor, and 2-year actuarial local progression-free rate was 96% and 2-year OS was 66%. Acute reactions of proton RT were well tolerated. Four patients died of hepatic insufficiency without tumor recurrence at 6–9 months. Three of these four patients had pretreatment indocyanine green retention rate at 15 min of more than 50% (Kawashima et al. 2005).

Recently, a multi-institutional phase II study was published in the USA, which included 44 patients of HCC and 37 with intrahepatic cholangiocellular carcinoma (ICC), all unresectable with a Child-Pugh score of A or B. The median maximum dimension was 5.0 cm (1.9–12.0 cm) for HCC patients and 6.0 cm (2.2–10.9) for ICC patients. Multiple tumors were present in 27.3% of HCC patients and in 12.8% of ICC patients. PVTT was present in 29.5% of HCC patients and in 28.2% of ICC. All received proton of 58.0 GyE in 15 fractions, for 3 weeks. The LC rate at 2 years was 94.8% for HCC and 94.1% for ICC. The OS rate at 2 years was 63.2% for HCC, and 46.5% for ICC (Hong et al. 2015).

University of Kobe treated HCC with proton or carbon beams. There were 242 HCC (with 278 tumors) irradiated with proton RT of 52.8–84.0 GyE in 4–38 fractions and 101 HCC (with 108 tumors) treated by carbon 52.8–76.0 GyE in 4–20 fractions. The 5-year LC and OS rates for all patients were 90.8% and 38.2%, respectively. The 5-year LC rates were 90.2% and 93%, and the 5-year OS were 38% and 36.3%, respectively, for proton and carbon ion. No patients died of treatment-related toxicities (Komatsu et al. 2011).

Table 3 summarizes the outcome of proton RT for liver cancers.

National Institute of Radiological Science (NIRS) is the first hospital to treat HCC with carbon ion. Kasuya recently reported a retrospective analysis of 124 HCC patients with a total of 133 lesions in NIRS. The fraction number was 12, 8, or 4 fractions with 4.5–13.2 GyE per fraction. The LC rates at 1 year, 3 years, and 5 years were 94.7%, 91.4%, and 90.0%, and OS at 1 year, 3 years, and 5 years were 90.3%, 50.0%, and 25.0%, respectively. The failure pattern was mainly in the liver outside of irradiated volume (77%), and out of liver (26%). There were no ≥3-point increase of Child-Pugh score observed (Kasuya et al. 2017). To shorten the treatment time NIRS further reduced the fraction number to two fractions with total doses of 32–45 GyE. Among 133 HCC treated there were 92% of Child-Pugh A patients and 8% Child-Pugh B, and 87% of UICC stages 1–2 and 23% of stages IIIA and IVA. The median maximum tumor diameter was 42 mm (14–140 mm). Acute toxicity was slight with only four cases of G3 hepatic toxicity and none of other G3 and G4–5 toxicity. So was the late toxicity. The LC rates were 98% and 90% at 1 year and 83% and 76% at

Table 3 Outcome of proton irradiation for hepatocellular carcinoma

Author	No. of pts	Dose	Toxicity	Efficacy
Chiba (2005)	162 (25 with PVTT)	Proton 72 GyE/16 fx (3.5–5 GyE/fx)	Late ≥G2, 3%	5-year OS 23.5% 5-year LC 86.9%
Nakayama (2009)	318	Proton 66 GyE/10 fx to 77.0 GyE/35 fx		OS: 1 year 89.5%, 3 years 64.7%; 5 years 44.6%; LC: 5 years 83.3%
Kawashima (2005)	30 (mean age of 70 years)	Proton 72 GyE/16 fx	Hepatic insufficiency (≤G3), 27%	2-year OS 66%, 2-year PFS 96%
Mizumoto (2011)	266	Proton 66–77 GyE/10–35 fx	*G* ≥3, 3%	OS: 1 year 87%, 3 years 61%, 5 years 48% (MST 4.2 years). LC: 1 year 98%, 3 years 87%, 5 years 81%
Bush (2011)	76	Proton 63 GyE/15 fx, 3 weeks	Acute toxicity: minimal	3-year PFS 60%; PFS: 36 months (30–42)
Komatsu (2011)	242	Proton 52.8–84.0 GyE/4–38 fx Carbon 52.8–76.0 GyE/4–20 fx		5-year LC 90.8%; 5-year OS 38.2%
Kim (2015a)	27	Proton 60 GyE/20 fx; 66 GyE/22 fx; 72 Gy/24 fx	No DLT (G3)	LPFS 3 years 79.9%, 5 years 63.9% OS 3 years 56.4%, 5 years 42.3%

DLT dose-limiting toxicity, *LPFS* local progression-free survival, *OS* overall survival, *PFS* progression-free survival, *PVTT* portal vein tumor thrombosis

3 years in the higher dose group (45 GyE) and the lower dose group (≦42.8 GyE), respectively. OS rates at 1 year were 95% and 96%, and 71% and 59% at 3 years in the higher dose group (45.0 GyE) and the lower dose group (≦42.8 GyE), respectively (Tsujii et al. 2014).

In 2015 Qi et al. did a meta-analysis to compare photon RT, SBRT, and charged particle RT (proton and heavy ion) in terms of toxicity and efficacy for HCC. It included 73 cohorts from 70 non-comparative observational studies. The study showed that OS in charged particle RT was higher than that in photon RT, but similar to that in SBRT. The RT toxicity was lower in charged particle RT than that in photon RT and SBRT (Qi et al. 2015).

Overall, proton and carbon ion RT yielded more promising outcome than photon RT and SBRT, especially less toxicity incidences.

2.1.4 Comments for the RT Role in BCLC Stage 0 and Stage A

Currently, surgery is the standard care for early stages of HCC, and 5-year OS was from 63.1% to 76.9%, which is the best among the all modalities available. The PEI and RFA have also been recommended as the options for early stage of HCC in most of the guidelines or consensus for HCC, although their efficacy is not as good as that in surgery (Table 4). However, those modalities have their limits. Surgery needs patients with good performance status and liver function reservation. PEI and RFA are preferred to treat small size of HCC, ideally <3 cm in diameter. Moreover, it was noticed that the recurrence at the tumor site after RFA increased with tumor size: 14% (<3 cm), 25% (3–5 cm), and 58% (>5 cm) (Mulier et al. 2005). In addition, the hepatic lesion location close to large vessels and bile ducts is the contraindication for RFA.

On the other hand, the new advanced RT techniques have shown the good LC and survivals, SBRT/SARB resulted in LC of 66–95% at 1 year, 51–92% at 3 years, and 59–73% at 5 years, respectively. Proton produces much better LC with 64.7–90.8% at 5 years, and OS of 64.7–83.3% at 3 years and 23.5–44.6% at 5 years, respectively. Carbon ion RT yielded even more promising results, and less irradiation-related toxicity. Those LC and OS were

Table 4 Outcome of RES, PEI, TACE, and RFA for early stages of hepatocellular carcinoma

Author	No. of pts	Tumor size (cm)	Treatment	Efficacy
Cho (2007)	116	≤233.1%	RES	OS: 1 year 94.8%, 3 years 76.5%, 5 years 65.6% DFS: 1 year 76.1%, 3 years 50.6%, 5 years 40.6%
	116	≤267.9%	PEI	OS: 1 year 95.7%, 3 years 73.5%, 5 years 49.3% DFS: 1 year 62.6%, 3 years 25.5%, 5 years 19.1%
Kagawa (2010)	62	≤5 cm	TACE + RFA	OS: 1 year 100%, 3 years 94.8%, 5 years 64.6% RFS: 1 year 64.5%, 3 years 40.1%, 5 years 18%
	55		RES	OS: 1 year 92.5%, 3 years 82.7%, 5 years 76.9% RFS: 1 year 75.6%, 3 years 41.1%, 5 years 36.4%
Nishikawa (2011)	69	≤3 cm	RES	OS: 1 year 100%, 3 years 81.4%, 5 years 74.6% RFS: 1 year 86.0%, 3 years 47.2%, 5 years 26.0%
	162		RFA	OS: 1 year 95.4%, 3 years 79.6%, 5 years 63.1% RFS: 1 year 82.0%, 3 years 38.3%, 5 years 18.0%
Guo (2013)	102	≤5 cm	RES	OS: 1 year 89.2%, 3 years 74.1%, 5 years 63.1% DFS: 1 year 59.8%, 3 years 42.4%, 5 years 40.8%
	94		RFA	OS: 1 year 94.7%, 3 years 74.7%, 5 years 49.8% DFS: 1 year 57.9%, 3 years 36.4%, 5 years 34%

RES resection, *PEI* percutaneous ethanol injection, *TACE* trans-artery chemoembolization, *RFA* radiofrequency ablation, *OS* overall survival, *RFS* relapse-free survival, *DFS* disease-free survival

comparable to those in PEI and RFA. In 2016 Wahl et al. did a comparison study between SBRT and RFA for early stages of HCC around 2 cm in diameter. They collected 161 patients treated by RFA, and 63 by SBR. OS rates at 1 year and 2 years were 75% and 53% after RFA, and 74% and 46% after SBRT, with no significant differences (Wahl et al. 2016).

In spite of lack of randomized studies, but large number of patients treated by RT, RT should have been proposed as one of the options for early-stage HCC. Actually, more attentions had been paid to RT recently. Klein and Dawson proposed that RT should be recommended to HCC BCLC stage 0-A, when they are not fit for surgery or PEI/RFA, and also as a bridge when the patients wait for liver transplantation (Klein and Dawson 2013). In 2016, Dhir listed the major treatment options available to patients with HCC, and added RT (conventional RT, SBRT, and proton) as a non-curative intent treatment (Dhir et al. 2016).

In 2014 American Society of Therapeutic Radiation Oncology (ASTRO) released model policies on proton RT, in which HCC was listed in Group 1 of malignancies for proton RT (ASTRO 2014). That means that radiation therapy society recognizes the role of proton RT in HCC.

Among the different RT techniques it was believed that conventional RT, SBRT, and particle RT yielded similar LC for tumor size of <5 cm in diameter, but proton and carbon ion RT can spare more normal liver, so more HCC patients would have chances to be irradiated, especially for tumors >5 cm in diameter, and deeply seated, like in hepatic hilar.

2.2 BCLC Stages B and C

For BCLC stages B and C TACE and sorafenib are the only treatments of choice in the majority of diagnosis and treatment guidelines for liver cancer. However, there are patients with PVTT and locoregional node metastases in BCLC stage C. For those patients, RT could also play a role of palliative treatment.

2.2.1 The Efficacy and Toxicity of RT for BCLC Stage B and Stage C

Kim and his colleagues have used IMRT to treat inoperable HCC (great vessel invasion or big size). The simultaneous integrated boost IMRT (SIB-IMRT) was employed for 53 patients. For 41 patients with tumor location of <1 cm to GI (low-dose fractionation, LD) 44 Gy in 22 fractions was delivered to clinical tumor volume

(CTV), which included the gross tumor and adjacent microinvasion, and simultaneously 55 Gy in 22 fractions, to gross tumor volume (GTV). For 12 patients with tumor away from GI (≥1 cm) (high-dose fraction, HD), total doses of 55 Gy in 22 fractions were given to CTV and 66 Gy to GTV. The toxicity was tolerable with no grade >3. The OS was 25.1 months, and the 2-year LPRS, RFS, and OS rates were 67.3%, 14.7%, and 54.7%, respectively. The HD group tended to have better 2-year LPFS (85.7% vs. 59%, $p = 0.119$), RFS (38.1% vs. 7.3%, $p = 0.063$), and OS (83.3% vs. 44.3%, $p = 0.037$) rates than the LD group (Kim et al. 2014). Later, Kim and his group continued their study, using the same SIB-RT technique, but delivered by proton. A total of 27 inoperable HCC had been treated with 60 GyE in 20 fractions to CTV and 72 Gy in 24 fractions to GTV. No dose-limiting toxicity (G3) was noticed. The LPFS and OS rates were 79.9% and 56.4% at 3 years, and 63.9% and 42.3% at 5 years, respectively (Kim et al. 2015a).

A prospective phase 2 multicenter trial of 3D-CRT was carried out in South Korea for unresectable HCC cases, who had viable tumor after TACE of no more than three courses. A total of 31 patients were enrolled. 3D-CRT was delivered at a median dose of 54 Gy by 1.8–2 Gy per fraction. The 2-year in-field LPFS, PFS, TTP, and OS rates were 45.2%, 29.0%, 36.6%, and 61.3%, respectively. Radiation-induced liver disease (RILD) was not observed. There were no treatment-related deaths or hepatic failure (Choi et al. 2014). Cho reported a total of 116 patients with locally advanced HCC treated by TACE + RT (67 patients) or sorafenib (49 patients). At baseline, the sorafenib group had more patients with a tumor size ≥10 cm, lymph node metastasis, and PVTT compared to the TACE + RT group. The OS in the TACE + RT group was significantly longer compared to the sorafenib group (14.1 vs. 3.3 months, $p < 0.001$). In the score-matched cohort, and TACE + RT group showed prolonged OS compared to the sorafenib group (6.7 vs. 3.1 months, $p < 0.001$). Multivariate analysis revealed that TACE + RT was the only independent prognostic factor associated with survival in the propensity score-matched cohort (HR = 0.172, $p < 0.001$). In 2015 a systematic review and a meta-analysis were published, which compared TACE alone to TACE plus RT for unresectable HCC, or with portal venous tumor thrombosis (PVTT) (Huo and Eslick 2015). A total of 25 trials (11 RCTs) including 2577 patients were collected. The analysis showed that patients receiving TACE plus RT showed significantly better survivals at 1, 2, 3, 4, and 5 years compared with TACE alone, although the incidence of gastroduodenal ulcers and hepatic injury was higher in patients with TACE plus RT than that in TACE alone.

Tang did a retrospective study of 371 patients with resectable HCC, but with PVTT. The patients were treated in two hospitals by surgical resection in one hospital (186 patients) or by 3D-CRT in the other hospital (185 patients). A total radiation dose of 30–52 Gy (median 40 Gy) was delivered by 3D-CRT to the tumor and PVTT. TACE was applied after surgery or 3D-CRT and then was repeated every 4–6 weeks. The median survival was 12.3 months for 3D-CRT and 10.0 months for surgery. The 1-, 2-, and 3-year OS rates were 51.6%, 28.4%, and 19.9% for 3D-CRT and 40.1%, 17.0%, and 13.6% for surgery, respectively ($p = 0.029$). Multivariate analysis showed that the extent of PVTT and mode of treatment were independent risk factors of OS. The most common death cause was the consequence of progressive intrahepatic disease (Tang et al. 2013).

Hou retrospectively collected 181 HCC with PVTT and/or inferior vena cava thrombosis (IVCTT), and those patients were irradiated by external RT with a median total dose of 50 Gy (30–60 Gy). The median OS was 10.2, 7.4, 17.4, and 8.5 months for patients with PVTT in portal vein (PV) branch, PV trunk, inferior vena cava (IVC), and PV plus IVC, respectively (Hou et al. 2012).

Kim did a single-center retrospective study which involved 557 patients with HCC with PVTT. They received TACE ($N = 295$), TACE and RT (TACE + RT) ($n = 196$), or sorafenib ($n = 66$). The TACE + RT group had longer median TTP and OS than the TACE-alone and sorafenib ($p < 0.001$). Multivariate analysis

revealed that TACE + RT was an independent predictor of favorable TTP and OS. In the matched cohort, the median TTP was significantly longer in TACE + RT than TACE alone (8.7 vs. 3.6 months, $p < 0.001$), and so were the OS (11.4 vs. 7.4 months, $p = 0.023$). In the matched 30 pairs of patients, TACE+RT yielded better TTP (5.1 vs. 1.6 months, $p < 0.001$) and OS (8.2 vs. 3.2 months, $p < 0.001$) than the sorafenib (Kim et al. 2015b).

Yoon analyzed 412 HCC patients with PVTT treated by TACE and 3D-CRT. Main or bilateral PVTT was observed in 200 (48.5%) patients. A median radiation dose of 40 Gy (21–60 Gy) was delivered in 2–5 Gy per fractions. CR was observed in 3.6% of patients and PR 24.3%. The progression-free rate was 85.6%. Median OS was 10.6 months, and the 1- and 2-year survival rates were 42.5% and 22.8%, respectively. G3-4 hepatic toxicity occurred in 41 patients (10.0%) during or 3 months after completion of radiotherapy, and G2-3 gastroduodenal complications in 15 patients (3.6%) (Yoon et al. 2012).

A randomized trial was carried out in South Korea with 90 HCC (Child-Pugh A, and median diameter of 9.7 cm) with portal vein invaded. They was evenly divided to sorafenib (400 mg bid) or TACE, every 6 weeks combined with RT of 45 Gy, in 2.5–3 Gy per fraction. Better outcomes were seen in TACE combined with RT, compared with sorafenib with 12-week PFS (86.7% vs. 34.3%, $p < 0.001$), 24-week overall respond rate (ORR) (33.3% vs. 2.2%, $p < 0.001$), median time to progression (mTTP) (31.0 vs. 11.7 weeks, $p < 0.001$), and median overall survival (mOS) (55 vs. 43 weeks, $p = 0.04$) (Yoon 2018). Therefore, for HCC with PVTT combined RT and TACE could be one option for BCLC B and C, besides sorafenib.

For BCLC stage C there were patients with metastases in lymph node, adrenal gland, bone, lung, and brain metastases, Chinese experience in treating them with RT also showed the palliative effect (Jiang and Zeng 2013).

2.2.2 Comments for the RT Role in BCLC Stage B and Stage C

All RT data shown above were from Asia, but they showed the promising local control and survivals and were superior to other treatment modalities, like TACE and sorafenib in terms of palliation. Sorafenib could be the treatment choice for BCLC stage C, although the palliative effect is very limited. One could ask why RT could not be one of the treatment options.

In the European guidelines for HCC, there was no role for RT for BCLC stage C at all. For NCCN guideline of hepatobiliary cancers the external RT was not strongly recommended to treat unresectable HCC until 2018 edition of NCCN. The recommendation level was raised to category 2A. However, ablation and arterially directed therapies were recommended much early as category 2A. Sorafenib efficacy was very limited, but the evidence was category 1.

In 2011, Chinese Ministry of Health issued a practice guideline of the diagnosis and treatment for liver cancer (Ministry of Health of the People's Republic of China 2011). RT was recommend for those patients with vascular invasion, or inadequate hepatic reserve. In addition, RT could be used as a palliative treatment for HCC with PVTT, or distant metastases to relieve pain. However, RT combined with other modalities, like TACE and sorafenib, is strongly recommended.

2.3 Summary of the Role of RT in the Management of HCC

As presented in the previous text, the modern RT techniques have shown their promising efficacies in the treatment for early-stage and locally advanced HCC. It is time to re-evaluate the role of RT in the management of HCC. However, it is a consensus that a clinical practice could be recommended in the diagnosis and treatment guidelines only after prospective randomized clinical trials have confirmed it. At present time the majority of RT data accumulated in the literature were retrospective or single-arm studies, and the follow-up time was not long enough. Nevertheless, the prospective randomized clinical trials cannot always be done in reality because of the patients' acceptance and financial obstacles. It is the task of RT society to accumulate a large number of patients treated

by RT, and repeat excellent outcome to convince liver cancer society to realize the role of RT in the management of HCC. Even the panel members for 2018 NCCN Guideline for Hepatobiliary Cancers had started to realize the important role of RT in the treatment of liver cancer. Therefore the evidence and consensus category of RT role for resectable, transplantable, and unresectable HCC was shifted from 2B in 2017 NCCN Guideline to 2A in 2018 edition. That meant that the panel members in North America uniformly believed that RT was appropriate. It is expected that the guidelines for liver cancers from big liver cancer societies in other continentals would change their attitude sooner and later.

3 Radiation Techniques

3.1 Target Moving Control

The target motion is a great challenge in liver cancer RT. The methods used to control the target motion include abdominal compression, active breath coordinator (ABC), and respiratory gating, like RPM from Varian and Enzai from Japan. It is evident that use of breath control management can reduce the dose to liver. As reported by Zhao (2008), compared to free breathing, ABC reduced the mean dose to normal liver (MDTNL) (16.9 Gy vs. 14.3 Gy), PTV (529 cm^3 vs. 781 cm^3), and V23 (45% vs. 30%). The predicted incidence of RILD by Lyman model was also decreased (1% vs. 2.5%). In Gong's dosimetric study when RapidArc was used, MDTNL, normal liver V10, V20, V30, and V40 were remarkably lower (10.23 Gy, 35%, 16%, 8%, and 5% at the end of exhale and 9.23 Gy, 32%, 16%, 8%, and 5% at the end of inhale, respectively) than 13.12 Gy, 46%, 24%, 13%, and 8% at free breathing (Gong et al. 2012). When the respiratory gating is used the beam on time is always chosen at the end of exhale. Therefore, both ABC and gating could decrease the normal liver dose and can be used for photon RT. There was no debate for breath control management, but the techniques need further improvement.

However, the use of respiratory gating was questioned for proton and heavy ion RT because the residual motion in the gating window would induce the changes of tissue density along the beam pass way so as to produce the range uncertainty, resulting in Bragg peak deposited in wrong position. Besides, the interplay effect produces another dose uncertainty for the moving target when beam scanning technique is used to deliver dose. To deal with the interplay effect re-scanning technique is used, but the interplay effect could not be get rid of totally.

3.2 RT Dose and Fractionation

As listed in Tables 1–3, the fraction size, fraction number, and total dose were quite various. For 3D-CRT and IMRT the conventional fractionation was used with 2 Gy per fraction and the total dose, up to 66 Gy, For SBRT/SARB large fraction size ranging from 7 Gy to 15 Gy per fraction was used, and the fraction number ranged from three to ten fractions. For proton RT, large fraction size had also been applied. However, Tsukuba experience was of reference value. Their dose fractionation was based on the tumor locations: 6.6 GyE per fraction for 10 fractions for peripheral tumor, 3.3 GyE per fraction for 22 fractions for tumors close to portal hepatis (<2 cm), and 2 GyE per fraction for 37 fractions for tumor close to gastrointestinal tract (<2 cm).

For carbon ion RT, NIRS has done a series of clinical trials on HCC with gradual reduction of fraction numbers, from 15 fractions to 2 fractions to find the most appropriate fractionation. Finally, 38.8–52.8 GyE was delivered in 2 fractions.

HCC was thought to be moderately radiosensitive, like epithelial carcinomas. However, there have not been widely accepted optimal dose fractionations for conventional or hypofractionated RT. It is the trend to reduce fraction number and shorten the irradiation period by increase of fraction size, like SBRT. By this way the tumoricidal effect would be enhanced because of the stronger tumor killing and less tumor repopulation. Nevertheless, the optimal RT fractionation has not concluded yet, but it is believed that the

biological effect dose (BED10) of >100 Gy estimated by L-O modal was necessary to control HCC. The recommended dose fractionation was 8–10 Gy per fraction for five fractions, when SBRT was used (Ohri et al. 2018). Therefore, the optimal RT fractionation has not been established yet.

3.3 The Normal Liver Irradiation Tolerance

The normal liver tolerance is strongly dependent on the fraction size, total dose, irradiated normal liver volume, and particularly hepatic underline disease, like hepatitis-induced cirrhosis. It is consensus that the RT tolerance for the liver with hepatic cirrhosis is much worse than that for liver with healthy background. Therefore, it should be always kept in mind when considering liver RT tolerance.

For the conventional fractionation, like 2 Gy per fraction, it was proposed as early as in 1965 by Ingold (1965) and in 1991 by Emami. The recommended liver tolerance doses were 30 Gy, 45 Gy, and 55 Gy for entire, two-thirds, and one-third of liver irradiation (Emami et al. 1991). These tolerances have been widely accepted and used as the dose constraint for liver RT. However this tolerance derived from photon irradiation for liver cancers, majority of which were metastatic liver cancers from gastric and colon cancers, and small percentage of patients were HCC. However, the live background in metastatic liver cancer patients was healthy, whereas predominant HCC patients are associated with hepatitis B- and C-induced hepatic cirrhosis. Therefore, it is believed that the above liver tolerance dose could not be applied to cirrhotic liver, and it should be reduced, but it is not known exactly to reduce it to what extent. Table 5 showed that the mean dose to normal liver (MDTNL) was higher in patients with RILD compared to those without it by conventional RT fractionation (1.8–2 Gy per fraction). MDTNL was less than 30 Gy in HCC patients, which demonstrated the poor RT tolerance for HCC patients.

From the modern RT treatment plan system the detailed dose distribution, especially inhomogeneous dose distribution in liver, could be obtained as dose volume histogram (DVH). More accurate liver tolerance dose could be withdrawn. Different from conventional fractionated RT, another term to define normal liver volume is used as "non-involved normal liver," or "nontarget normal liver" (NTNL), which is the amount of total liver volume minus GTV. Table 6 summarizes the proposed dose constraints by hypofractionated RT with large fraction size of around 5 Gy per fraction, but with different endpoints to evaluate the hepatic toxicity, including RILD (classic or nonclassic), frequency of occurrences of CTCAE grade 3–4, or decline of Child-Pugh score. One could define what dose constraint of liver tolerance by readers was. Liang (2006) analyzed 109 HCC patients with hepatitis-induced hepatic cirrhosis, who were irradiated by 3D-CRT with median of 4–6 Gy per fraction. The liver tolerance dose (defined as no RILD) was mean dose

Table 5 Mean normal liver dose and radiation-induced liver disease in conventional fractionated radiation therapy

Study group	Patient number	Diagnosis	Baseline Child-Pugh class	Prescribed dose per fractionation to tumor	Crude percentage of RILD	Mean normal liver dose[a] in patients with vs. without RILD
Michigan (1995, 2002)	203	PLC + MLC	CP-A 203	1.5 Gy bid	9.4% (19/203)	37 Gy vs. 31.3 Gy
Cheng (2002)	68	HCC	CP-A 53 CP-B 15	1.8–2 Gy, qd	17.6% (12/68)	25.04 Gy vs. 19.65 Gy
Kim (2007)	105	HCC	CP-A 85 CP-B 20	2Gy, qd	12.3% (13/105)	25.4 Gy vs. 19.1 Gy

PLC primary liver cancer, *MLC* metastatic liver cancer, *HCC* hepatocellular carcinoma, *CP-A/B* Child-Pugh class A/B, *bid* twice fractions a day, *qd* one fraction a day, *RILD* radiation-induced liver disease

[a]Normal liver volume: liver volume minus gross tumor volume

Table 6 The proposed dose constraints of non-involved liver irradiated by hypofractionated irradiation

	Patient number	Tumor dose (Gy)/ fraction number	Endpoint of hepatic toxicity	Dose constraint	References
Child-Pugh A					
Mean dose	101 93	36 (24–54)/6 53.6 ± 6.6/11	C-P score ≥2[a] RILD	<20 Gy <23 Gy	Velec (2017) Liang (2006)
DVH	93		RILD	V5 < 86%, V10 < 68% V15 < 59%, V20 < 49% V25 < 35%, V30 < 28% V35 < 25%, V40 < 20%	Liang (2006)
	42	55 (30–60)/5(3–6)	C-P score decline	V25 < 32%	Dyk (2015)
	85	39–50/3–5	RIHT ≥ 1[b] RIHT ≥ 2[b]	V15 ≤ 21.5% V15 ≤ 33.1%	Su (2018)
Child-Pugh B					
Mean dose	21 16	40/5 53.6 ± 6.6/11	RIHT G3–4[c] RILD	≤8.82 Gy <6 Gy	Lasley (2015) Xu (2006)
DVH	21	40/5	RIHT G3–4	V7.37 < 33% V < 2.5 Gy = 810.8 cc V < 5 Gy = 1024.1 cc V < 7.5 Gy = 1149.7 cc V < 10 Gy = 1293.0 cc V < 12.5 Gy = 1432.0 cc V < 15 Gy = 1515.9 cc	Lasley (2015)

DVH dose volume histogram, *C-P score* Child-Pugh score, *RIDL* radiation-induced liver disease
[a]Child-Pugh score dropped ≥2
[b]Radiation-induced hepatic toxicity C-P score dropped ≥1, or ≥2
[c]Radiation-induced hepatic toxicity G3-4 (CTCAE)

to non-involved liver of 23 Gy. From the analysis of dose volume histogram (DVH), a tolerable DVH curve was regressively drawn for HCC with Child-Pugh A (Fig. 1).

QUANTEC recommended a liver dose constraint (Table 7). However, this dose constraints should be used with cautions as the different underlying liver, and the inhomogeneous dose distribution would make the dose constraint uncertain. For SBRT/SARB the recommended constraint is just for RT plan with fraction number from 3 to 6.

In summary, for conventional fractionated RT the liver tolerance is known, but is not totally known for hepatic background with different degrees of hepatic injury. For hypofractionated RT, what is the liver tolerance as the dose constraints for treatment planning needs further investigation in clinical practice, with special attentions to the factors, which influence RT tolerance, including the severity of hepatic cirrhosis, inhomogeneity of dose distribution, and fraction size.

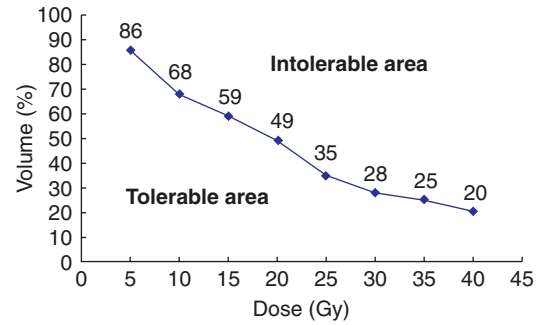

Fig. 1 A tolerable dose volume histogram (DVH) for primary liver cancers irradiated by hypofractionated irradiation

3.4 RT Method

Currently 3D-CRT, IMRT, RapiArc (RA), and helical tomotherapy (Tomo) are commonly used in clinic to treat HCC. However, the advantages and disadvantages and the appropriate indications for those RT techniques are under investigation.

Table 7 Quantitative analysis of normal tissue effects in the clinic (QUANTEC) recommendations for dose constraints during external beam radiation therapy (RT) to the liver

	Liver metastases	Primary liver cancer	Comment
Whole-liver RT	≤30 Gy, 2 Gy/fx 21 Gy/7 fx	≤28 Gy, 2 Gy/fx 21 Gy/7 fx	Whole-organ prescription dose
Partial-liver RT, conventional fractionation	≤32 Gy	≤28 Gy	Mean normal liver[a] dose for tumor dose ≤2 Gy/fx
SBRT, 3–6 fx	<15 Gy/3 fx <20 Gy/6 fx	<13 Gy/3 fx <18 Gy/6 fx CP B:<6 Gy/4–6 fx	Mean normal liver[a] dose
	At least 700 cc normal liver <15 Gy/3 fx At least 800 cc normal liver <18 Gy/3 fx		Critical volume model Only for Child-Pugh class A

SBRT stereotactic body radiation therapy, *fx* fraction, *GTV* gross tumor volume, *CP* Child-Pugh class
[a]Normal liver: the total volume of liver minus the gross tumor volume

Gong did a dosimetric study to compare 3D-CRT, IMRT, and RA at the end inspiration hold (EIH), end expiration hold (EEH), and free breathing (FB) techniques. RA resulted in better conformity index and homogeneity index than IMRT and 3D-CRT for the three breathing techniques ($p < 0.05$). The RA and IMRT significantly reduced the mean dose, V20, V30, and V40 of normal liver compared to 3D-CRT, while the V5 and V10 in RA were higher than in IMRT. In addition, the treatment time by RA was equal to 3D-CRT, which was significantly shorter than IMRT (Cheng et al. 2002).

Jin compared Tomo to fixed-beam IMRT plan in a dosimetric study. It was found that Tomo was better than fixed-beam IMRT in homogeneity index (1.35 vs. 1.27, $p < 0.001$) and conformity index (1.24 vs. 1.30, $p = 0.008$), but the mean NTNL-V15Gy (NTNL-V15) decreased remarkably in the fixed-beam IMRT plan (34.8%) compared to 41.1% in Tomo plan ($p < 0.001$). The mean total liver dose was also lower in the fixed-beam IMRT plan than Tomo plan (13.3 Gy vs. 15.6 Gy) ($p < 0.001$). The probability of RILD was estimated based on mean NTNL-V15Gy. The mean NTNL-15Gy were 41.1% and 34.8% for Tomo and fixed-beam plan, and the correspondent probabilities of RILD were 0.216 and 0.115, respectively (Song et al. 2015).

Hsieh in a dosimetric study showed that Tomo was better in uniformity than coplanar IMRT, and less normal liver V30Gy (21% in IMRT vs. 17% in Tomo). However, the V10Gy was higher with Tomo than IMRT (72.5% in Tomo vs. 64.8% in IMRT) (Hsieh et al. 2010).

Zhao (2016) recently published dose comparisons among 3D-CRT, IMRT, and Tomo. They found no significant differences between the mean dose to NTNL, liver V5 to V30, except for V20 between IMRT and Tomo. However, the above parameters in 3D-CRT were higher than IMRT and Tomo.

A retrospective study was done to compare 3D-CRT and image-guided IMRT for HCC by Yoon (Yoon 2014). 3D-CRT was used in 122 patients and IMRT 65 patients. IMRT delivered higher doses than 3D-CRT (mean BED 62.5 Gy vs. 53.1 Gy, $p < 0.001$). IMRT showed significantly higher 3-year OS (33.4% vs. 13.5%, $p < 0.001$), PFS (11.1% vs. 6.0%, $p = 0.004$), and IFFS (46.8% vs. 28.2%, $p = 0.007$) than 3D-CRT. In spite of retrospective study it really showed the advantage of IMR over 3D-CRT.

It was evident that 3D-CRT was inferior to IMRT, RA, and Tomo in terms of homogeneity and conformity, and dose to liver. RA and Tomo produced better dose homogeneity and conformity compared to IMRT, especially for intrahepatic multiple lesions, but at the expense of large volume of low dose to the normal liver. The advantage of fixed-beam IMRT is the decrease of low-dose volume of normal liver. Which method is better?

In liver cancer irradiation, especially for HCC, RILD is a fatal irradiation complication

and no medications or treatments are available. Therefore, prevention of RILD is paramount when liver irradiation is planned.

What are the risk factors to produce RILD? Besides liver cirrhosis, the dose to NTLD is critical. Mean dose to NTNL is most important. However, the parameters from DVH are also useful to predict RILD. Son (2013) found that the normal liver V15 was the most significant factor for RILD. Liang also reported that V20 was the most significant dosimetric parameter for the risk of RILD, and the cutoff value was 48.5%. It had suggested that the large volume effect of the liver was still important (Guha and Kavanagh 2011; Pan et al. 2010). Therefore, reducing the volume of low-dose region in NTNL is crucial to prevent RILD. Overall, RA and Tomo deliver a larger volume with a low dose than IMRT. Thus, use of IMRT could be the choice in HCC irradiation, especially when low-dose volume is big, like NTNL-V15 and –NTNL-V20. IMRT with the limited beams is likely to reduce low-dose volume.

The histopathologic feature of RILD is veno-occlusive disease (VOD), which results in classic RILD. In the nonclassic RILD, hepatocellular loss and dysfunction secondary to radiation-induced mitotic catastrophe of regenerating hepatocytes are the features. To prevent RILD, besides decreasing dose to NTNL it is very important that the normal liver should be protected from irradiation as much as possible and keep a part of normal liver not irradiated. It is well known that the liver has very strong capability to proliferate once it is damaged, like after surgery. Animal studies on rats have shown that normal liver could be stimulated to proliferation after partial irradiation; moreover, low-dose irradiated liver could also proliferate (Zhao et al. 2009; Ren et al. 2012). Further studies on rats with thioacetamide-induced cirrhosis liver showed the same phenomenon, and the nonirradiated and low-dose irradiated cirrhotic liver could repopulate, but the capability was worsened (Gu et al. 2011). Although the low-dose irradiated liver has the capability to proliferate, however, it is not known what is the dose threshold, after which the liver loses its proliferation capability. Therefore, it is wise to protect a part of liver totally avoiding irradiation so as to make this part of liver proliferating to compensate the loss of liver function after irradiation injury. Considering the issue of liver proliferation, it is preferable to use fixed-beam IMRT to treat HCC, instead of RA and Tomo, as the entire liver is explored to irradiation in RT and Tomo. However, this proposal needs to be confirmed by clinical practice.

In recent years, particle RT, proton, and carbon ion RT have been used for liver cancer more frequently than before. To compare the dose distributions by photon, proton, and carbon ion a dosimetric comparison study was done in eight HCC patients treated in Shanghai Proton and Heavy Ion Center (Wang n.d.). It showed that proton and carbon ion RT delivered much less doses to NTNL, right kidney, and stomach than X-ray, when tumor dose of 60 GyE was delivered with similar dose coverage (Fig. 2 and Table 8). Comparing carbon ion to proton, carbon ion gave less dose to kidney, but more dose to stomach (Table 8). For carbon ion, besides less dose to nontarget liver than proton, it has more advantage over proton for liver tumor location adjacent to gastrointestinal tract. Figure 3 shows that carbon ion delivers less doses to duodenum and colon (Wang et al. 2018). The reason for the less dose to gastrointestinal tract is the sharp penumbra of carbon ion, which is smaller than proton. Therefore, when the gastrointestinal tract locates laterally to the axis of beam direction, carbon ion hits it less. From the dosimetric comparison carbon ion has more dosimetric advantages than proton in less doses to nontarget liver and gastrointestinal track.

Although the patient number treated by proton and carbon ion RT was much less than by photon the outcome has shown better local control and survival, and less hepatic toxicity. However, due to unavailability of the facilities and the expensive cost their application has been limited. Moreover, their optimal dose and fractionation have not been concluded yet.

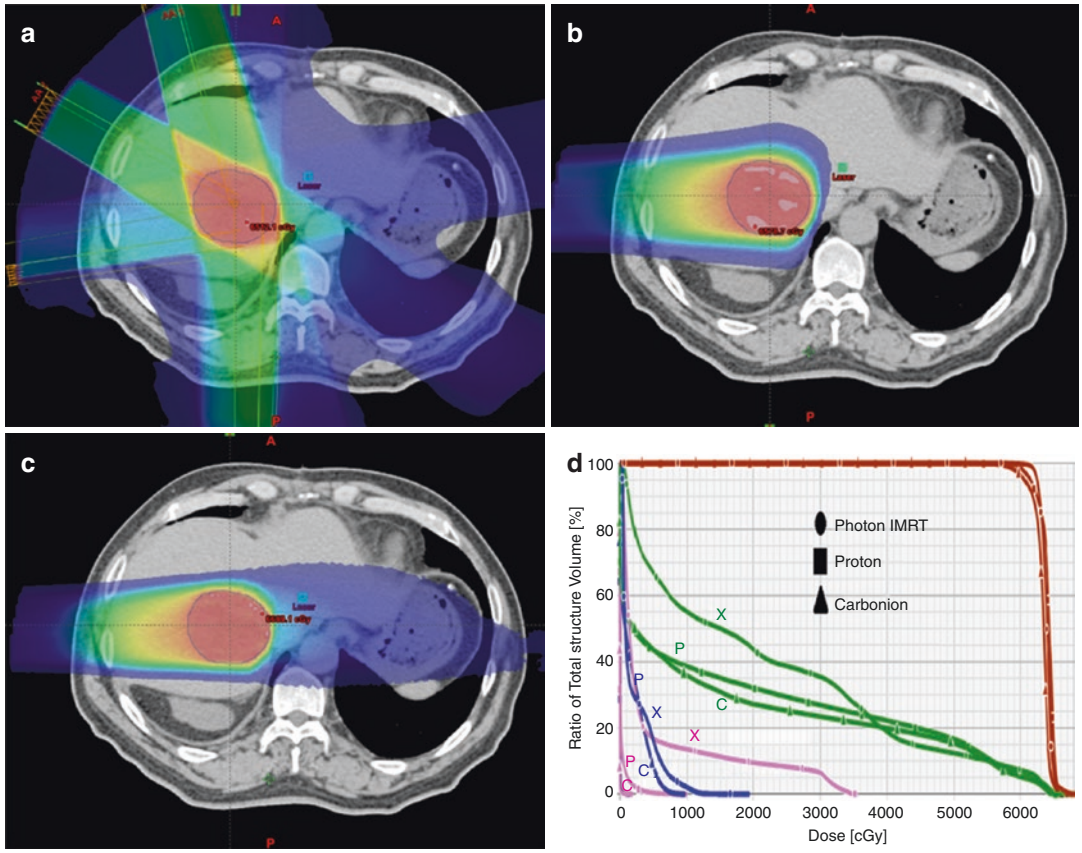

Fig. 2 Dose distribution comparison in one hepatocellular carcinoma patient. (**a**) Photon IMRT: 6 Gy/fraction for 10 fractions; (**b**) intensity-modulated proton irradiation: 6 GyE/fx for 10 fractions; (**c**) intensity-modulated carbon ion irradiation: 6 GyE/fx for 10 fractions; (**d**) dose-volume histograms for target (brown), nontarget liver (light green), kidney (pink), and stomach (blue) irradiated by photon (X), proton, and carbon ion, respectively

Table 8 Comparison of doses to liver, right kidney, and stomach using intensity-modulated irradiation (IMRT), intensity-modulated proton radiation therapy (IMPT), and intensity-modulated carbon ion radiation therapy (IMCT) for 8 hepatocellular carcinoma patients treated in Shanghai Proton and Heavy Ion Center

Dose parameter	Photon (X)	Proton	Carbon ion
ITV coverage (V95%)	99.8 ± 3.2	99.6 ± 4.8	99.9 ± 3.7
Nontarget liver			
Mean dose (GyE)	23.17 ± 4.30*	17.00 ± 2.92$^{\#}$	15.49 ± 2.62$^{\$}$
Kidney			
Mean dose (GyE)	5.91 ± 10.7^{+}	2.84 ± 8.46$^{\&}$	2.00 ± 9.41$^{=}$
Stomach			
Max dose (GyE)	29.92 ± 7.10**	2.61 ± 13.55$^{\#\#}$	10.03 ± 12.79$^{\$\$}$

All figures shown are mean ± sd

t-test: * vs. #, $p = 0.00$; * vs. $, $p = 0.00$; # vs. $, $p = 0.01$

+ vs. &, $p = 0.02$; + vs. =, $p = 0.01$; ** vs. ##, $p = 0.00$; ** vs. $$, $p = 0.00$; ##, vs. $$, $p = 0.01$. For all other comparisons between 2 parameters p were >0.05

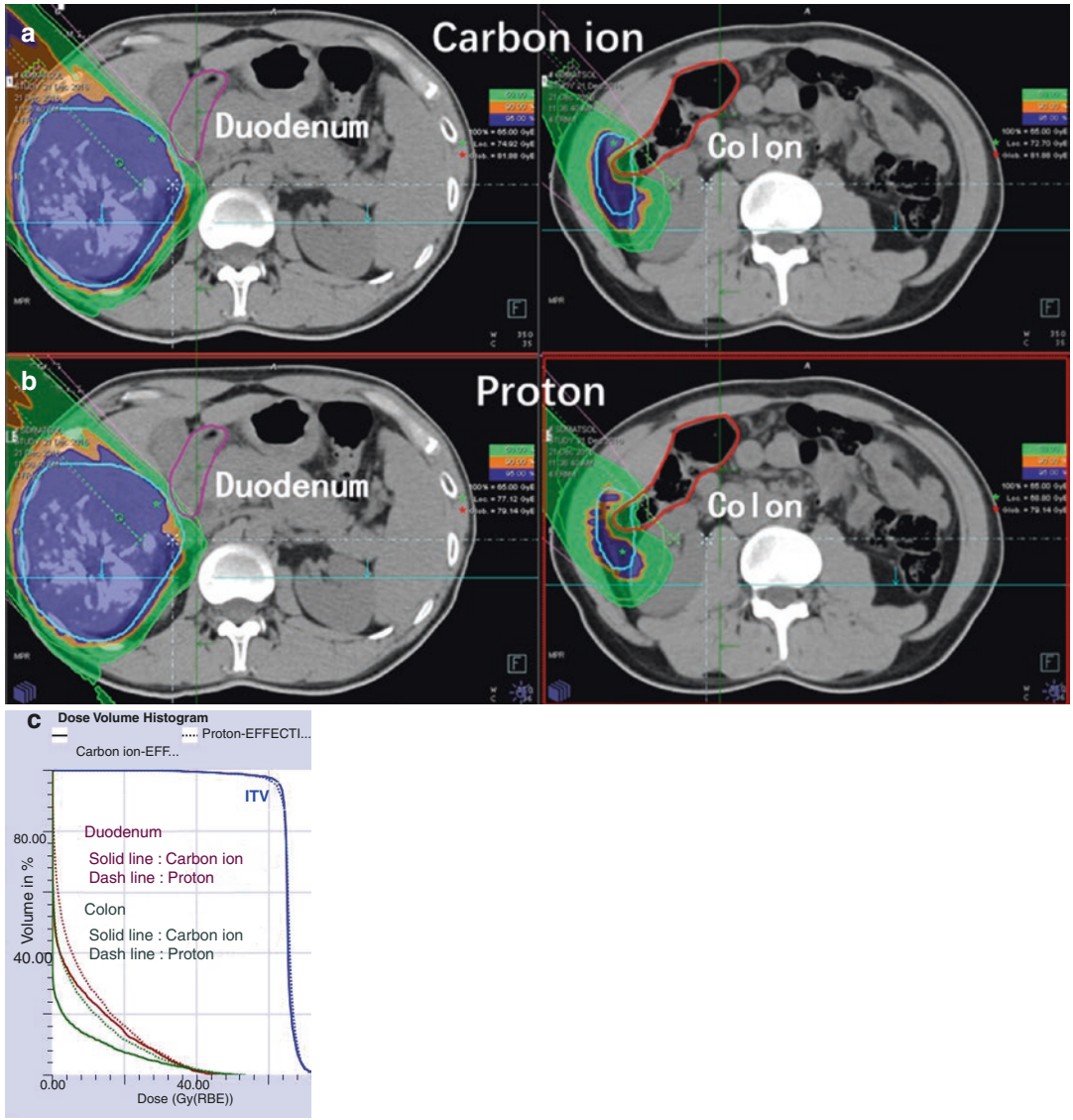

Fig. 3 Dose distributions of intensity-modulated proton and intensity-modulated carbon ion irradiation for liver cancer located adjacent to gastrointestinal tract. (**a**) Carbon ion; (**b**) proton; (**c**) dose volume histogram

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