



Efficacy and safety of radiotherapy for primary liver cancer

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Abstract: Primary liver cancer includes hepatocellular carcinoma (HCC, 75–85%) and intrahepatic cholangiocarcinoma (10–15%). The vast majority of patients with primary HCC are not candidates for surgical treatment. Surgical resection, liver transplantation and percutaneous puncture are effective potentially curable treatments for patients with early stage liver cancer. Radiation therapy is a non-surgical alternative treatment that has generally been used to treat patients with advanced liver cancer, although its use in the potentially curative setting is increasing. Radiotherapy is a non-invasive local treatment which works through ionizing radiation. This review summarizes the efficacy and safety of commonly used radiotherapy methods, and reviews three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT), stereotactic body radiotherapy (SBRT), volume-modulated arc therapy (VMAT), and internal radiation therapies, for primary liver cancer (in particular for HCC).

Keywords: Primary liver cancer, hepatocellular carcinoma (HCC); radiotherapy; internal radiation therapy; tumor

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Introduction

Primary liver cancer

Primary liver cancer includes hepatocellular carcinoma (HCC) (75–85% of cases) and intrahepatic cholangiocarcinoma (10–15% of cases), and other less common tumors, such as fibrolamellar HCC (1). Primary liver cancer generally has a high potential for vascular and metastatic spread and a poor prognosis. The average life span after diagnosis is 6–20 months, with 3- and 5-year survival rates of 72% and 50% respectively after surgery, and the 5-year survival rate from 48% to 61% after liver transplantation, both for patients with early stage HCC (2–4).

HCC is one of the most common causes of cancer-related death globally. Its incidence is highest in areas with

high incidence of hepatitis B (HBV) and hepatitis C (HCV), particularly in Southeast Asia and Sub-Saharan Africa (5–8). According to the 2019 GLOBOCAN estimated, there are approximately 42,030 new liver cancer cases diagnosed, and 31,780 liver cancer deaths (9). This review mainly focuses on the usage of radiotherapy in HCC.

Treatment of primary liver cancer

For HCC, surgical resection and/or liver transplantation remain the first-line treatment options for radical treatment with the goal of cure. Most patients with HCC do not present with symptoms until their tumor is at an advanced, often incurable, stage. The vast majority of patients are not candidates for surgical treatment. The current surgical

resection rate is only 20% (10). According to Guide to the Treatment of Hepatocellular Carcinoma from the American Association for the Study of the Liver Diseases (AASLD), surgical resection, liver transplantation and percutaneous puncture are effective for very-early and early stage HCC patients (Child-Pugh A, tumor diameter <3 cm); for whom the median OS is longer than 60 months, and the 5-year survival rate is 50–70% (3,11,12). Unfortunately, patients with macro and/or microvascular invasion, as well as patients with multifocal tumor, have a worse prognosis despite surgical resection, with a 5-year recurrence rate of 70% or higher (13,14). Non-surgical treatments such as transcatheter arterial chemoembolization (TACE), chemotherapy, molecular targeted drugs, are generally reserved for treatment of these patients with intermediate and advanced liver cancer (15–17). There is emerging experience and ongoing clinical trials of the use of radiotherapy to treat such patients with intermediate and advanced HCC.

Radiotherapy for primary liver cancer

Radiotherapy is a non-invasive local treatment that works through ionizing radiation that causes direct and indirect DNA double strand breaks (18). Liver tumors are sensitive to radiation treatment, with moderate to high radio sensitivity, next to very radiosensitive tumors of the bone marrow and lymphatic tissue and normal tissues such as the bone marrow and kidney (19). Mechanically, the energy of ionizing radiation directly or indirectly acts on biological macromolecules such as nucleic acids, proteins, enzymes, etc., and through irradiation of water to produce ionization that reduce or disable their normal function, and lead to unreparable double strand DNA breaks (20). The normal liver has a strong ability to regenerate, and the spared normal tissue can compensate for the radiation-induced focal damaged liver, by the hepatic cell proliferation of the spared liver.

Radiotherapy for HCC has undergone a series of technical advances over the decades from whole-liver wide field low dose irradiation, to local field irradiation, moving strip radiotherapy, and hyper-fractionation radiotherapy that now can be delivered quite conformally around focal liver tumors. Prior to the 1990s, large volume liver irradiation led to damage to normal liver, which frequently led to radiation-induced liver disease (RILD), liver failure or even death if excessive doses were delivered to the full liver (21). Therefore, there was a delay in the use of focal

radiation therapy used with curative intent. With the application of three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT), and stereotactic body radiotherapy (SBRT), the accuracy of the lesion targeting was significantly improved while the radiation dose on the surrounding normal tissues was able to be substantially reduced. With recent advanced imaging and radiation treatment technologies, the risk of serious complications has been substantially reduced. At present, radiotherapy has become an indispensable part of comprehensive treatment for HCC (22–25). It is included as a prioritized treatment across early, intermediate and advanced HCC patients in some country guidelines [e.g., Korean (26)], but reserved as treatment options only if other standard treatments are not feasible in other treatment guidelines [e.g., NCCN (27)].

Radiotherapy can be classified into external radiation therapy and internal radiation therapy (using a variety of radiation sources) (18). External radiation therapy mainly includes SBRT, 3DCRT, IMRT and volume-modulated arc therapy (VMAT), using photon-based radiation therapy. Protons and carbon ions have also been used to treat patients with liver cancer, but they are more expensive and less widely available (28–30). Internal radiation therapy includes ^{90}Y microsphere therapy, ^{131}I monoclonal antibody, radioactive iodinated oil and ^{125}I particle implantation, often delivered via the hepatic artery. Percutaneous brachytherapy has also been used to treat liver cancer (31). This article analyzes the effectiveness and safety of various radiotherapy techniques in different stages of liver cancer (in particular for HCC). A summary of studies regarding the response rate and overall survival of radiotherapy for primary liver cancer is listed in *Table 1*.

External radiotherapy

Three-dimensional conformal radiation therapy (3DCRT)

In recent years, 3DCRT has been commonly used in liver cancer (32). This therapy is based on advances in computer computation, optimization and virtual reconstruction technology. Radiation target volumes and field shapes and angles are designed with the help of a radiotherapy treatment planning software system that calculated dose in a patient model based on a CT scan of the patient in treatment position. The target dose is calculated according to the tolerance doses of adjacent normal tissues and the underlying liver (33).

CRT allows the sparing of normal tissues such as the liver, by reducing acute and late adverse reactions, and it thus substantially improves the therapeutic ratio when used to treat patients with liver cancer (34). A challenge of 3D-CRT is that liver movement occurs due to respiratory, which impacts the accuracy in locating and irradiating the liver tumor. If the irradiated liver volume is too high, the risk of liver toxicity may increase (35). More recently, strategies have become available to reduce the negative impact of respiratory motion of the liver such as liver immobilization through active breath hold, gating radiation therapy to one phase of the breathing cycle or tracking the radiation beam with the moving liver (36,37).

3DCRT has been used to treat early stage liver cancer, with local control rates of 71.4% (38) to 93.8% (39) at more than one month, and one year overall survival of 73.6% (40) to 81.1% (39). Outcomes are best in patients with single and small HCCs (less than 10 cm) compared to those with larger, multifocal cancers with vascular invasion (39). Mornex *et al.* had treated 25 patients with a single HCC (diameter <5 cm) or with two tumors (diameter <3 cm) using a total dose of 66 Gy (33 daily fractions over 6 weeks). This treatment achieved a local control rate of 92% at more than three months (24). Another 3DCRT study included 198 HCC patients with tumors smaller than 10 cm and not eligible for surgical resection or local ablation therapy. One the group was treated with a median total dose of 52 Gy (with a fraction of 5.0–7.0 Gy, three fractions a week), the other group received a median total dose of 53 Gy (with a fraction of 2.5–4.9 Gy, three fractions a week); the former had a better survival. Overall, for the entire study population, the one year overall survival was 73.6%, which suggests that 3DCRT is an effective ablative therapy for small HCC (40). The local control rate of 71.4% in small HCC (size <5 cm) was conducted by Park *et al.* (38). Similar studies using 3DCRT for small HCC showed favorable results (41,42).

For advanced liver cancer, 3DCRT has been associated with good short-term efficacy.

3DCRT is one of the most effective treatments for HCC with portal-vein/inferior-vena-cava tumor invasion, thrombosis or emboli. Tang *et al.* analyzed 371 patients with liver cancer with portal vein tumor emboli who received surgery (186 cases) and 3DCRT (185 cases). The 1-, 2-, and 3-year survival rates of the radiotherapy group were 51.6%, 28.4%, and 19.9%, respectively; the survival rates of the surgery group were 40.1%, 17.0% and 13.6%,

respectively (43). Lim *et al.* treated 45 HCC patients with portal vein tumor emboli with 3DCRT from 38 to 65 Gy in fractions. The results demonstrated that 6.7% patients achieved CR, 55.6% had PR, 31% showed SD, and PD occurred in 6.7%. No RILD was found during the long-term survivors (44). Similarly, Kouloulis *et al.* reported 9 patients with 60% response rate and a total survival of 24 months (45). Yoon *et al.* analyzed the efficacy of radiation therapy combined with TACE based on 412 patients with portal vein tumor emboli, and reported that 3DCRT had a local control rate of 27.9% (3.6% CR and 24.3% PR); the 1-year and 2-year survival rates were 42.5% and 22.8%; the local control from radiation therapy was an independent prognostic factor, and the median survival time of those who had stable or responding HCC was 19.4 months (46).

IMRT

IMRT is a newer technology developed on the basis of 3DCRT. Using optimization software, based on multi-field irradiation, the dose intensity of each field within larger fields can be varied, and the radiation dose in the target area may be more evenly distributed, and more tightly surrounding the target volume, sparing concave or convex adjacent normal tissues, which is beneficial for protecting important sensitive organs. It is more suitable for treating tumors with irregular three-dimensional shapes. The disadvantages of IMRT are the longer exposure time and poor tolerance in patients with severe illness (47,48).

Most of the IMRT series have focused on advanced liver cancer patients, with a local control rate from 30% to 50% for advanced HCC (49,50). For tumors with a margin less than 1 cm adjacent to or involved in the hilar vascular trunk, IMRT is helpful for those who will receive surgery. IMRT improved the 3-year OS and disease-free survival in HCC patients receiving narrow margin hepatectomy. A study analyzed 181 patients with central liver cancer showed that proximal resection marginal plus IMRT for patients had similar achieve OS and recurrence-free survival to those with wide resection margins (50). Retrospective analysis of 136 patients with microvascular invasion (MVI) demonstrated that radiotherapy following hepatectomy could improve survival outcomes in comparison with TACE or conservative treatment. This treatment strategy is highly effective for patients with a narrow surgical margin (51). A prospective randomized study was conducted by Yu *et al.* which recruited 119 HCC patient who had narrow-margin (<1 cm) hepatectomy and showed a higher trend

Table 1 Summary of studies regarding the response rate and overall survival of radiotherapy for primary liver cancer

Application	Year	Authors	Case number	Methods	CR	PR	RR	1-year OS	2-year OS	3-year OS	5-year OS
3DCRT in early stage liver cancer	2019	Fang <i>et al.</i>	111	53 Gy (a fraction of 2.5–4.9 Gy) 3 times/week	–	–	–	57.70%	31%	–	18.90%
			87	52 Gy (a fraction of 5.0–7.0 Gy) 3 times/week	–	–	–	73.60%	43.70%	–	33.30%
	2004	Zeng <i>et al.</i>	54	3DCRT	–	–	76%	71.50%	42.30%	24.00%	–
	2007	Zhou <i>et al.</i>	50	TACE + 3DCRT	–	18%	–	–	–	–	–
	2014	Jung <i>et al.</i>	20	3DCRT	–	–	90.90%	–	87.50%	–	–
3DCRT in advanced liver cancer	2013	Lim <i>et al.</i>	61	3DCRT	68.90%	–	–	81.10%	–	58.40%	–
	2014	Chen <i>et al.</i>	78	TACE + 3DCRT	–	–	71.8%	78.48%	55.12%	25.64%	–
	2005	Shim <i>et al.</i>	38	TACE + 3DCRT	–	83.30%	–	–	36.80%	–	–
	2014	Yoon <i>et al.</i>	122	3DCRT	–	–	–	–	–	13.50%	–
	2015	Wang <i>et al.</i>	55	Hypo-fractionated 3D-CRT	47.30%	43.60%	90.90%	83.60%	–	31.7%	–
3DCRT in HCC with portal vein/inferior vena cava tumor emboli			55	Conventional 3D-CRT	38.20%	49.10%	87.30%	68.8 %	–	13.90%	–
	2016	Hou <i>et al.</i>	64	3DCRT	1.60%	51.60%	53.10%	35.80%	–	–	–
	2014	Lee <i>et al.</i>	46	3DCRT	6.50%	26.10%	32.60%	66.80%	–	–	–
	2015	Fujino <i>et al.</i>	41	3DCRT	5%	24%	29.00%	–	–	–	–
	2012	Rim <i>et al.</i>	45	3DCRT	6.70%	55.60%	62.30%	63.70%	–	–	–
IMRT in advanced liver cancer	2012	Yoon <i>et al.</i>	412	TACE + 3DCRT	3.6%	24.3%	27.90%	42.50%	22.80%	–	–
	2014	Yoon <i>et al.</i>	65	IMRT	–	–	–	–	–	33.4%	–
	2013	Kong <i>et al.</i>	22	IMRT	18.20%	54.50%	72.70%	86.40%	69.10%	–	–
	2017	Jiang <i>et al.</i>	45	IMRT	8.90%	48.90%	57.80%	93.35%	73.30%	–	–
	2019	Byun <i>et al.</i>	101	IMRT ≥72 Gy	–	–	–	62%	–	–	–
			536	IMRT <72 Gy	–	–	–	51%	–	–	–
	2015	Wang <i>et al.</i>	116	IMRT + hepatectomy	–	–	–	–	–	89.1%	–

Table 1 (Continued)

Table 1 (Continued)

Application	Year	Authors	Case number	Methods	CR	PR	RR	1-year OS	2-year OS	3-year OS	5-year OS
IMRT in HCC with portal vein/inferior vena cava emboli	2013	Kong <i>et al.</i>	8	IMRT	-	50.00%	50%	-	-	-	-
	2016	Hou <i>et al.</i>	54	IMRT	5.60%	64.80%	70.40%	59.30%	-	-	-
	2019	Sun <i>et al.</i>	26	IMRT + hepatectomy	-	-	-	76.90%	19.20%	11.50%	-
VMAT in small HCC	2018	Jeong <i>et al.</i>	119	VMAT-based SBRT	89.20%	6.50%	95.70%	99.2%	-	83.80%	-
VMAT in HCC portal vein/inferior vena cava emboli	2013	Wang <i>et al.</i>	138	VMAT	11%	53%	64%	-	-	-	-
	2014	Wang <i>et al.</i>	20	VMAT	36.40%	31.80%	68.20%	-	-	-	-
	2013	Mian <i>et al.</i>	41	VMAT-based SBRT	36.60%	39.00%	75.60%	50.30%	-	-	-
SBRT in early stage liver cancer	2014	Sanuki <i>et al.</i>	185	SBRT	-	-	-	95%	83%	70%	-
	2017	Su <i>et al.</i>	82	SBRT	-	-	-	96.30%	-	81.80%	70.00%
	2015	Yamashita <i>et al.</i>	79	SBRT	46%	35%	81%	-	39.9%	-	-
	2010	Kwon <i>et al.</i>	42	SBRT	59.6%	26.20%	86%	92.9%	-	58.60%	-
SBRT in advanced liver cancer	2017	Gkika <i>et al.</i>	47	SBRT	-	-	-	Median OS =9 months			
SBRT in the centrally located HCC	2018	Lazarev <i>et al.</i>	53	SBRT	-	-	-	53.50%	39.10%	-	-
SBRT in HCC with extensive portal vein thrombosis	2018	Shui <i>et al.</i>	70	SBRT/SBRT + TACE	9.70%	69.40%	79.10%	40.00%	-	-	-
	2014	Kang <i>et al.</i>	101	SBRT/SBRT + TACE	28.70%	58.40%	87.10%	58.8%	-	-	-

in adjuvant RT group of one-, 3-, and 5-year recurrence-free survival rates than that in control group (52). Besides, combined application of IMRT and TACE can significantly improve the prognosis of HCC patients. A study observed 26 liver cancer patients with portal tumor thrombus (87% were in III–IV stage) and found the patients under the combined treatment of IMRT and TACE (the median dose of radiotherapy was 50 Gy, 44–70 Gy) had an effective rate of 64.8% and a median survival of 20.2 months (53).

Volumetric modulated arc therapy (VMAT)

VMAT is a dynamic IMRT method with the advantages of delivering irradiation via a rotating gantry. It may be used in combination with active breathing coordinator (ABC) to immobilize the liver. When compared with 3DCRT or IMRT, it is superior in dose conformity. VMAT provides a more accurate target area, with lower organ-endangering dose and less radiation liver injury (8,54,55). Wang *et al.* treated 138 HCC patients (88.4% of patients in AJCC stage III or IV) with VMAT, with radiotherapy doses of 45, 60, and 66 Gy (once 1.8 or 2 Gy) and finally evaluated 108 patients. All participants were classified as BCLC stage A–C. They showed 11% CR, 53% PR, 29% SD, and 6% PD cases at a total follow-up of maximum 28 months. The median survival time was 10.6 months, the local control rate at 6 and 12 months were 95% and 93.7%, respectively; no serious toxic events occurred (54).

SBRT

SBRT is a radiotherapy method that combines stereotactic technology and 3DCRT. With image guidance and respiratory motion management technology, SBRT can accurately target the tumor area and launch a high dose in the centre of the tumor, while the dose outside the target area decreases sharply. Thereby, normal tissue close around the tumor can be well protected from radiation. SBRT allows irradiation to be delivered in fewer fractions than conventional radiation therapy (1 to 6 over one to two weeks, versus 25 to 35 over 5 to 7 weeks) and requires high precision delivery with daily image guidance (56,57).

SBRT is most successful in the treatment of smaller liver cancers, and early reports have focused on early stage HCC. Although the local control rate is reduced in larger tumors, the majority of tumors larger than 10 cm, are controlled following modest dose SBRT 1 to 2 years post SBRT (58). Andolino *et al.* followed up 60 patients with HCC who had received SBRT. Their median tumor diameter was 3.2 cm, the dose was 42 Gy/3 fractions, the local control

rate was 90% for two years, the 2-year PFS rate was 48%, and the 2-year OS rate was 67%; as expected, no RILD events occurred (59). Kwon *et al.* treated 42 HCC patients with doses from 30 to 39 Gy/3 fractions; they observed a CR of 60% and PR of 26%, and the 1- and 3-year PFS rates were 72% and 67.5%, respectively (60). In another retrospective study, patients with Child-Pugh A (n=137) received radiotherapy doses of 40 Gy/5 fractions and patients with Child-Pugh B (n=48) liver dysfunction received 35 Gy/5 fractions. The 3-year local control rates were 89% and 91%, the OS rates were 72% and 66% (61). Takada *et al.* used SBRT to treat 50 small-HCC patients and confirmed that the dose of 30 Gy/5 fractions was safe and effective for patients with cirrhosis (62).

There is an overlap in the indications of SBRT and radiofrequency ablation therapy for small HCC, and they were compared in some studies. Rajay Urgur *et al.* analyzed the prognosis of non-chemotherapy-and-non-metastatic HCC treated by radiofrequency ablation or SBRT in the National Cancer Database (NCDB) from 2004 to 2013. There were 3,684 patients receiving radiofrequency ablation and 2% receiving SBRT. The OS in the radiofrequency ablation group was significantly better than that in the SBRT group, and this advantage remained after pairing with propensity scores ($P < 0.05$) (63). However, a study by Wahl *et al.* retrospectively analyzed the prognosis of 224 patients with non-surgical-and-non-metastatic HCC. Among them, 161 were treated with radiofrequency ablation, and 63 were treated with SBRT. The results showed that the radiofrequency ablation treatment group had 83.6% PFS rate within 1 year and 80.2% within 2 years, respectively; while the SBRT group showed 97.4% and 83.8% PFS rate respectively, there were no significant differences between two groups. Also, there were no differences in the OS rates. However, when the diameter was greater than 2 cm, the SBRT group had a better outcome than radiofrequency ablation treatment (64).

For patients with advanced HCC, SBRT has also been useful. Chan *et al.* performed SBRT on 16 advanced HCC patients at a dose of 45 Gy/10 fractions. The local control rate was 91%, and the 1- and 3-year survival rates were 62% and 28%, respectively (65). Other studies showed that the local control rate of SBRT for patients with larger, more advanced HCC, often invading the portal vein, ranged from 63% to reached 87%; the median survival time ranged from 12.9 to 17 months; the 1-year and 3-year survival rates were 87% and 55%, respectively (58,66), with a risk from liver toxicity ranging from 10% to 30%.

Proton and heavy ion radiotherapy

Proton and heavy ion radiotherapy have a potential benefit of less low dose splash to adjacent normal tissues, which may be helpful for deep liver tumors and/or for patients with impaired liver function (67). The proton and carbon ion radiotherapy doses are deposited within the body in a Bragg peak, with a sharp falloff of dose in the normal tissues beyond the target volume. Proton and heavy ion radiotherapy have some other potential advantages to photons, in addition to the sharp drop in dose after the Bragg peak; these include a higher linear energy transfer, high relative biological effectiveness, and low oxygen effect. By adjusting the energy, the Bragg peak may be localized at the depth of the tumor, which kills the tumor cells and protects the normal tissues around the tumor (68). Nakayama applied proton radiotherapy to treat 47 HCC patients at a dose of 72.6 Gy/22 fractions or 77 Gy/35 fractions. In this work, the median OS time was 33.9 months, the 3-year local control rate reached 88.1%, and the total 3-year survival rate was 50%. In the end, 6.4% and 2.1% of patients were reported grade 2 and 3 gastrointestinal reactions, respectively (69). Lee *et al.* studied 27 HCC patients with portal vein tumor thrombi using proton radiotherapy (50 to 66 Gy/20 to 22 fractions). They acquired an outcome of 55.6% PR, 37% SD, and 7.4% PD cases (70). Imada *et al.* carried out a prospective study enrolling 64 HCC patients with portal vein tumor thrombus. Among them, 18 liver tumors were close to the thrombus (<2 cm), and the remaining 46 tumors were far away from the thrombus. The radiation dose was set as 52.8 Gy/4 fractions. In the end, the 5-year survival rate of 18 patients (whose tumors were close to the thrombus) was 22.2%, and the local control rate reached 87.8%. For 46 patients whose tumors were far away from the thrombus, the 5-year survival rate was 34.8% and local control rate was 95.7%, respectively (71).

Internal radiotherapy

Internal radiation therapy takes advantages of the natural cavity or tissue space of the human body to directly place or implant a radioactive source. Using catheters, the radioactive source was sent into the target and high-dose radiation can be applied in a low volume (72). At present, the internal radiation treatment of primary liver cancer mainly uses selective internal radioembolization therapy (SIRT), including ^{90}Y microsphere, ^{131}I monoclonal antibody, radioactive iodinated oil, and ^{125}I particle

implantation. Among them, application of ^{90}Y microsphere radiotherapy can prolong the survival of HCC patients and can downgrade large tumors to meet the liver transplantation standards (73–75). There is evidence that SIRT can provide the survival benefit is comparable to TACE (76). When compared with SBRT, SIRT also showed similar results in overall and disease-specific survival benefit in unresectable HCC (77). More randomized trials need to conduct to compare SIRT with various modalities to therapy HCC in the future.

Conclusions

Radiotherapy is becoming an indispensable component of comprehensive treatment of primary HCC. The optimal role of radiotherapy, the exact radiotherapy strategy, as well as ideal sequencing are largely unknown; factors to consider in multi-disciplinary decision making include the tumor number, volume, location, and whether there is portal venous tumor invasion, in addition to liver function and patient performance status. Randomized trials of radiation therapy are ongoing and make help to elucidate the role of radiation therapy in this setting.

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