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REVIEW

Role of radiotherapy in the management of hepatocellular carcinoma: A systematic review

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Abstract

Many patients with hepatocellular carcinoma (HCC) present with advanced disease, not amenable to curative therapies such as surgery, transplantation or radiofrequency ablation. Treatment options for this group of patients include transarterial chemoembolization (TACE) and radiation therapy. Especially TACE, delivering a highly concentrated dose of chemotherapy to tumor cells while minimizing systemic toxicity of chemotherapy, has given favorable results on local control and survival. Radiotherapy, as a therapeutic modality of internal radiation therapy with radioisotopes, has also achieved efficacious tumor control in advanced disease. On the contrary, the role of external beam radiotherapy for HCC has been limited in the past, due to the low tolerance of surrounding normal liver parenchyma. However, technological innovations in the field of radiotherapy treatment planning and delivery, have provided the means of delivering radical doses to the tumor, while sparing normal tissues. Advanced and highly conformal radiotherapy approaches such as stereotactic body radiotherapy and proton therapy, evaluated for efficacy and safety for HCC, report encouraging results. In this review, we present the role of radiotherapy in hepatocellular carcinoma patients not suitable for radical treatment.

Key words: Hepatocellular carcinoma; Radiotherapy; Radio-embolization; Hyperthermia; Review

Core tip: Treatment of hepatocellular carcinoma is challenging since it is usually associate with underlying liver morbidity. The role of radiotherapy has evolved. The combination settings with radioisotopes, transarterial chemoembolization, hyperthermia, stereotactic radiotherapy and charged particles, support the efficacy and safety of the radiation therapy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for the vast majority (85%-90%) of primary liver cancers[1] with the latter representing approximately 4% of annual cancer diagnosis. Although HCC is the fifth most common cancer in men and the seventh in women, its poor prognosis makes it the third leading cause of cancer-related death worldwide[2,3]. Overall, there are 500-1000000 new cases per year, causing 600000 deaths globally per year[4]. It is characterized by a great geographic variability, with the highest rates in East and South-East Asia and Sub-Saharan Africa[5]. Environmental factors have a predominant role in the etiology of HCC. The majority of cases are related to exposure to hepatitis B and C viruses[6]. Other risk factors include alcohol, aflatoxins, diabetes and non-alcoholic fatty liver disease, as well as immune-related factors such as autoimmune hepatitis and primary biliary cirrhosis[7].

Treatment of HCC is quite challenging since it is usually associated with underlying liver disease. Available curative treatment options include surgical resection, transplantation and radiofrequency ablation[8-10]. These are suitable for carefully selected patients with early stages of disease who may have a 5-years survival of 70% after treatment[11]. However, only 1/3 of HCC patients are detected with a disease amenable to curative therapy. Partial hepatectomy is the treatment of choice for patients medically fit for a major operation who have a solitary tumor, adequate liver reserve and no evidence of gross vascular invasion[12,13]. Transplantation is considered for patients who meet the Milan criteria: a single tumor $\leqslant$ 5 cm or 2-3 tumors $\leqslant$ 3 cm each, no macrovascular involvement and no extrahepatic disease. However, from 2013, the United Network for Organ Sharing administered the Organ Procurement and Transplantation Network (OPTN) criteria by using radiologic staging (up to three OPTN class 5A or 5B HCCs, each 1 cm or larger and 3 cm or smaller in diameter, or one OPTN class 5B HCC measuring 2 cm or larger and 5 cm or smaller in diameter)[14]. Liver transplantation offers a chance to cure the tumor and the underlying cirrhosis[15,16]. Although transplantation is a cornerstone in the treatment of HCC, the relative shortage of donors highlights the need of other therapeutic approaches.

Radiofrequency ablation (RFA) can be used with a curative intend for patients with lesions up to 5 cm, if they are properly located at a safety distance from major vessels or major bile duct and away from diaphragm and other intraabdominal organs. Randomized controlled trials have already reported comparable survival rates of RFA to resection[17] for carefully selected patients. However, even if the recent meta analysis of Duan confirms that there is no significant difference in 1-year overall survival between resection and radiofrequency ablation, it also shows that the long-term efficacy of surgery is better than that of RFA[18]. Recently, artificial ascites technique has been used to prevent visceral damage when RFA is applied for subdiaphragmatic tumors or HCC adjacent to vital organs.

Results are less satisfactory for more advanced stages of the disease, not amenable to curative therapies. Available options are local therapies such as transarterial chemoembolization (TACE) and radiation therapy. The purpose of TACE is to increase the exposure of tumor cells to cytotoxic agents and to induce ischemic necrosis. This approach has given encouraging results on local control and survival for patients ineligible for curative therapy[19,20]. However, TACE is relatively contraindicated in patients with main portal vein thrombosis and Child-Pugh (CP) Class A, increasing the need for another effective local therapy. Internal radiation therapy with the use of radioisotopes has been tested and achieved efficacious treatment control and encouraging results on survival according to literature[21,22].

Finally, sorafenib is the only molecular agent approved for the treatment of patients with advanced hepatocellular carcinoma. Sorafenib is a multikinase inhibitor that targets vascular endothelial growth factor receptor, platelet-derived growth factor receptor and RFA. The use also of CTLA-4 showed good safety profile and antitumor activity, supporting further investigation[23]. Studies have shown an overall survival benefit with diarrhea, fatigue, hand-foot skin reaction and rash being the most common drug-related adverse events[24,25].

Traditionally, the role of external beam radiation therapy (EBRT) has been limited to the palliation of HCC metastases associated with distressing symptoms. There are numerous reports of bone[26,27], lymph node[28,29] and soft tissue[30] metastases that were successfully treated with external beam radiation therapy, as shown in Table 1. HCC has been considered a radioresistant tumor for a long time. The dose delivered by conventional external beam radiotherapy could not exceed 30 Gy on the whole liver as this is the threshold for radiation-induced liver disease. However, this dose level is far less than standard tumoradical doses for most solid tumors. Technological advances in the field of radiotherapy precision delivery and sparing of normal tissues have given the opportunity of dose escalation. Nowadays, radiotherapy is gaining ground in the treatment of advanced-stage HCC patients, irrespectively of tumor location, with promising results.

OPTIONS OF RADIOTHERAPY

Internal radiotherapy

Internal radiotherapy is the delivery of radioisotopes either percutaneously or through transarterial approach. Yttrium-90 (Y^{90}) is a pure beta emitter isotope that decays to stable 90 Zr with a physical half-life of 64.2 h. It has been applied to unresectable HCC by intratumoral

Table 1 Palliative radiotherapy for hepatocellular carcinoma metastatic sites

Ref.	Metastatic lesion treated	Patient (*n*)	Total dose, fraction size	Response	Median survival
Yamashita *et al*[122] (Retro)	LNs	28	46-60 Gy, 2Gy	PR: 64%; CR: 18%	13 mo
Zeng *et al*[29] (Retro)	LNs	62	40-60 Gy, 2 Gy	PR: 37.1%; CR: 59.7%	9.4 mo
He *et al*[121] (Retro)	Bone	30	8-60 (median 40) Gy	96.7% pain relief	8.6 mo
Seong *et al*[26] (Retro)	Bone	51	12.5-50 (median 30) Gy	73% pain relief	5 mo
Kaizu *et al*[123] (Retro)	Bone	57	20-65 (mean 43) Gy	83.8% pain relief	6 mo

PR: Partial response; CR: Complete response; Retro: Retrospective study; LNs: Lymphnodes.

injection of glass microspheres by percutaneous assess to the hepatic artery[31,32]. This approach, called radioembolization, is based on the different arteriolar density between the hypervascular HCC and the normal liver parenchyma. Arterial administrated Y^{90} microspheres depose selectively in tumor nodules and limit tumor dose to surrounding normal liver[33]. This technique can be used in downstaging large tumors to bring within transplantable criteria, in patients with portal vein thrombosis and in the palliative setting[34]. Overall, radioembolization of unresectable HCC with Y^{90} is associated with acceptable toxicity and favorable median survival time[35-38]. Radioembolization-induced liver disease, defined as jaundice and ascites appearing 4-8 wk after treatment, has been described in the literature[39]. It is more common in cirrhotic patients with an incidence of < 10%.

Holmium-199 (Ho^{199}), moslty beta and a little gamma emission with a half-life of 26.8 h, has also been tried in chitosan complex either intratumorally or *via* transarterial approach. Sohn *et al*[40] reported, in a phase Ⅱ study, a 78% response rate of intraarterial Ho^{199} for single HCC with an acceptable toxicity, especially for tumors 3-5 cm. Percutaneous holmium injection also showed promising results with complete tumor necrosis in 91.7% of tumors < 2 cm (phase Ⅱb clinical trial)[41].

Iodine-131 (I^{131}), mostly beta and a little gamma emission with a half-life of 8 d, has been applied in a form of I^{131}-Lipiodol[42]. Intraarterial administration yields responses in 17%-92% of patients[21]. Fifty patients with advanced HCC given intraarterial injection of I-Lipiodol were compared to 36 untreated patients[43]. The I^{131}-lipiodol was associated with a survival benefit (32 wk *vs* 8 wk for the untreated group) and 1 year survival rate was 32% *vs* 8% for the untreated group.

Overall, encouraging results on efficacy and safety of radioisotope therapy for HCC have been reported. This approach is reasonable for large, inoperable tumors and small, inoperable tumors not amenable to percutaneous therapy as well as for tumor downstaging before transplantation or surgery[44].

Three-dimensional conformal radiotherapy

Since there is no standard therapy for Radiation-induced liver disease (RILD), radiation therapy to liver lesions is an acceptable option as long as normal tissue complication probability does not exceed tumor control probability. Technological advances in the field of treatment planning and radiotherapy delivery have provided the means to deliver tumoradical doses to a well-defined liver lesion more precisely and safely, thus achieving an acceptable therapeutic ratio.

Irradiation technique of three-dimensional conformal radiotherapy (3DCRT) uses three dimensional imaging data sets (contrast enhanced computed tomography studies) for the accurate delineation of the HCC target volume and surrounding normal tissues, such as normal liver parenchyma, kindey and duodenum. Treatment plans are individualized and use multiple fields to precisely irradiate the tumor and spare normal tissues.

3DCRT has been tested as an alternative treatment option for cirrhotic HCC patients not eligible for curative therapies such as surgical resection, liver transplantation and radiofrequency ablation.

Early attempts to treat unresectable hepatocellular carcinomas with radiation therapy combined it with intraarterial hepatic radiation sensitizer, fluorodeoxyuridine, with encouraging results[45,46]. The study of Ben-Josef *et al*[47], confirmed the hypothesis that high dose conformal radiotherapy (median dose of 60.75 Gy, 1.5 Gy twice daily) combined with hepatic arterial floxuridine could improve the survival of patients with intrahepatic cancer ineligible for surgical resection or ablation[47]. Moreover, total radiation dose was the only significant factor for survival.

Later on, three studies (two phase II and one retrospective) assessed the efficacy of 3DCRT[48-51].

Data from Mornex *et al*[48] (phase Ⅱ study) confirmed the efficacy of radiation therapy (RT), delivering 66 Gy at 2 Gy/fr to selected cirrhotic patients with one nodule ⩽ 5 cm or two nodules ⩽ 3 cm. Tumor response was observed for 92% overall, with 80% for complete response[48]. CP-A patients tolerated treatment well while 22% of CP-B patients experienced gr 4 toxicity. After a mean follow-up of 29 ± 9 mo, recurrence rate was 22% and 41% for lesions inside and outside the irradiated volume, respectively.

Liu *et al*[51] studied 45 patients with CP-A and -B cirrhosis who had either failed with or were unsuitable for TACE[50]. The response rate after a median radiation dose of 50.4 Gy was 61.4%. Survival rates at 1, 2 and 3 years were 60.5%, 40.3% and 32%, respectively. American Joint Committee on Cancer stage, portal vein thrombosis, pretreatment alpha-fetoprotein (AFP) level and total RT dose had a significant impact on overall survival. On the contrary, age, gender, karnofsky performance status, CP class, tumor size or the number of tumors did not

significantly influence survival.

Overall, the worldwide availability of 3DCRT, the opportunity to treat multiple lesions in a single course along with its non-invasive feature, as well as the favorable results in the literature makes it an appealing therapeutic approach for patients ineligible for curative interventions.

3DCRT and TACE

TACE has an advantage on survival in comparison with supportive treatment[52] and is an effective measure for prolonging the survival in selected patients with limited cirrhosis and early stage tumors[53,54]. However, TACE alone cannot always achieve complete tumor necrosis (range 40%-100%). Viable tumors remain in and around the capsule increasing the possibility of recurrence[55,56]. TACE alone has a median response rate of 38%, while complete response and partial response are at the range of 0%-35% and 3%-62%, respectively[57]. Moreover, TACE is relatively contraindicated for patients with main portal vein thrombosis. To overcome the above mentioned limitations of TACE, the combination of TACE with EBRT has been tested. The rationale for this approach is that radiotherapy can either eradicate residual hepatic tumor after TACE or increase the effectiveness of TACE by eradicating portal vein thrombi.

Seong *et al*[58] investigated the combination of TACE with 3DCRT in unresectable HCC. Thirty patients received local RT with 44 ± 9.3 Gy in daily 1.8 Gy fractions, starting 7-10 d after TACE. The combination therapy had acceptable toxicity and achieved a response rate of 63.3%. One and 3-year survival rate were 67% and 22.2%, respectively.

Data from the series of Guo *et al*[59], that compared chemoembolization alone with the combination of TACE and radiotherapy, confirmed the superiority of the combined modality for the treatment of large hepatocellular carcinomas. The study included 76 patients with unresectable HCC treated with RT and TACE and 89 patients in the control group treated with TACE alone. The response rate was significantly higher in the first group (47.4% *vs* 28.1%, $P < 0.05$). The combined therapeutic approach was also significantly superior for overall survival (64.1% and 28.6% for 1 and 3-year survival *vs* 39.9% and 9.5%, respectively). Finally, the metaanalysis of Meng *et al*[60] with 1476 patients showed that TACE plus RT seems superior to TACE alone, optimizing survival and tumor control rates.

For patients with portal vein thrombosis the combination treatment has also given favorable results. Ishikura *et al*[61] reported a response rate of 50% for 20 patients receiving 50 Gy in 25 fractions after TACE for HCC with portal vein thrombosis[61]. A study from Japan confirmed the feasibility and efficacy of TACE combined with radiation therapy delivering 60 Gy in daily fractions of 2 Gy[62]. Survival rate at 1 and 2 years was 40.6% and 10.2%, respectively while an objective response was observed in 57.9% of patients.

Overall, the literature supports the feasibility and efficacy of this combined approach for HCC patients with or without portal vein thrombosis[63-67].

Stereotactic body radiotherapy

Advanced technologies, such as stereotactic body radiotherapy (SBRT), have raised a new interest in HCC radiotherapy. SBRT is a highly conformal technique of non-coplanar RT delivered in a small number of large fractions. It is characterized by a high dose delivery to the target volume and a rapid fall off outside the target, thus sparing surrounding normal tissues. The use of SBRT presupposes accurate patient immobilization and positioning, precise target localization and image-guided techniques to improve set up accuracy and delivery of the treatment. Moreover, when treating liver lesions, techniques that account for tumor motion with respiration and breathing control devices should be available. Patients with lesions near the bowels are not optimal candidates for SBRT since there is the risk of gastrointestinal perforation and bleeding. On the contrary, SBRT can be used to treat lesions not amenable to surgery or ablation such as those adjacent to the central biliary system[68].

It's a fact that the few patients eligible for transplantation have to face the long waiting list for donor organ availability. The role of SBRT in this field is of paramount importance. There are several reports proving SBRT as a bridge to transplantation to be a highly effective therapeutic approach with low toxicity profile[69-71].

O' Connor *et al*[71] studied 10 patients with 11 HCCs and a median tumor size of 3.4 cm that received SBRT (median dose 51 Gy in 3 fractions) as a bridge to transplantation. Complete response rate was 27%. The remaining tumors decreased in size or remained stable and no patient dropped off the wait list because of tumor progression. After a median follow up of more than 5 years, overall survival and disease free survival were both 100%. Although 40% of patients experienced acute toxicity that was mainly grade I nausea, vomiting, fatigue and abdominal discomfort. There was no grade 3-5 toxicity.

A Belgian study gives high 1- and 2-year control rates of 95%, delivering 45 Gy in 3 fractions[72].

According to the study by Jang *et al*[73], there is a dose response relationship for local control and overall survival with SBRT for HCC[73]. The study included 108 patients with HCC < 7 cm that were unsuitable for resection or local ablation and had incomplete response to TACE. After a 30 mo follow up, 2-year local control and overall survival were 87% and 663%, respectively. Overall, 54 Gy in 3 fractions is an acceptable dose to achieve local control for lesions < 7 cm. However, the optimal dose for a certain local control rate differs according to tumor size. A tumor ⩽ 5.0 cm requires a 51.1 Gy dose for a 2-year local control probability of 90%, while a larger tumor requires 61.2 Gy for the same local control probability.

SBRT has been also used in combination with TACE.

Table 2 Stereotactic body radiation therapy studies related to hepatocellular carcinoma, published the last five years

Ref.	Study design	Patient (*n*)	Median tumor size	Dose, No. of fractions	Median follow up (range), in months	Local control
Cárdenes *et al*[77]	Prosp Phase Ⅰ	17	34 mL (8-95)	CP-A: 36-48 Gy/3 fr CP-B: 40 Gy/5 fr	24 (10-42)	100%
Louis *et al*[72]	Retro	25	48 mL (7-363)	45 Gy/3 fr	12.7 (1-24)	95% (1 yr)
Kwon *et al*[79]	Retro	42	15 mL (3-82)	30-39 Gy/3 fr	28.7 (8.4-49.1)	72% (1 yr) 67.5% (3 yr)
Seo *et al*[80]	Retro	38	40.5 mL (11-464)	33-57 Gy/3-4 fr	15 (3-27)	66% (2 yr)
Andolino *et al*[69]	Retro	60	29 mL (2-12) 3.2 cm (1-6.5)	CP-A: 44 Gy/3 fr CP-B: 40 Gy/5 fr	27 (2-52)	90 (2 yr)
Huang *et al*[81]	Retro	36	4.4 cm (1.1-12)	37 (25-48) Gy/4-5 fr	14 (2-35)	88% (1 yr) 75% (2 yr)
Bae *et al*[82]	Retro	35	131 mL (21-2189)	45 (30-60) Gy/3-5 fr	14 (1-44)	69% (91 yr) 51% (93 yr)
Bujold *et al*[78]	Prosp Phase Ⅰ/Ⅱ	102	117 mL (1-1913) 7.2 cm (1.4-23.1)	36 (24-54) Gy/6 fr	31 (2-36)	87% (1 yr)
Xi *et al*[90]	Retro	41	65 mL (± 48)	36 (30-48) Gy/6 fr	10 (4-25)	95%
Sanuki *et al*[127]	Retro	185	8 mL (1.5-65)	CP-A: 40 Gy/5 fr CP-B: 35 Gy/5 fr	24 (3-80)	91% (3 yr)

Prosp: Prospective; Retro: Retrospective; fr: Fraction; CP: Child-Pugh class of liver disease.

Kang, in a phase Ⅱ study, investigated the efficacy and safety of SBRT for inoperable HCC after incomplete TACE for tumors < 10 cm. In this study patients received 3 fractions to a total dose of 42-60 Gy after 1-5 TACE. Complete remission after 6 mo of SBRT was observed to 38.3% of patients and partial response was at the same rate. The overall 2-year local control rate was 94.6%[74]. These results are in line with other series from Korea and Japan reporting encouraging local control rates[75,76].

Overall, studies have indicated that stereotactic body radiation therapy is a safe and effective modality treatment for HCC[77-82], as shown in Table 2. It can be applied for lesions not eligible for surgery or percutaneous ablation such as those located at a central portal area or just below the diaphragm and those adjacent to a great vessels or the biliary system.

National Comprehensive Cancer Network guidelines version 2.2014 have incorporated external beam radiation therapy, either 3DCRT or SBRT, to the therapeutic algorithm for HCC. SBRT can be safely considered for patients with 1-3 lesions, with sufficient uninvolved liver parenchyma and CP-A liver disease.

Stereotactic body radiation therapy for HCC with portal vein tumor thrombosis

A special issue raising questions about the optimal treatment of HCC is the high incidence of portal vein tumor thrombosis (PVTT). Although at the time of diagnosis only 6.5% of patients have demonstrable portal vein thrombosis[83] in autopsy series the incidence is reported to be as high as 44%-62.8%[84,85]. PTVV is associated with intrahepatic tumor spread and liver function deterioration.

First attempts to treat this group of patients with 3DCRT gave encouraging results of overall response rate in the range of 44.7%-62.3%[86-88]. However, the role of radiotherapy for this group of patients has become more appealing with the development of advanced radiotherapy techniques that deliver higher doses to liver lesions while reducing normal tissue exposure.

Kim *et al*[89] evaluated the efficacy of Helical Tomotherapy for patients with HCC in combination with PVTT in whom other treatment modalities were not indicated. Treatment protocol combined radiotherapy (50 Gy in 10 fractions with helical Tomotherapy) with Capecitabine 600 mg/m^2, given twice daily during radiotherapy. Computed tomography was used for response evaluation of 35 patients with thrombi either in the main trunk of portal vein (51.8%) or in the first or second order branches. Complete and partial response was reported on 14.3% and 28.6% of patients, respectively, while a 5.7% of patients had disease progression. Response was significantly different between CP class A and B ($P = 0.01$) and Japan integrated staging score ($P = 0.026$). Although tumor thrombi in the main trunk were significantly associated with inferior survival, results were favorable for those achieving complete response (13.9 mo).

Xi *et al*[90] reported on the results of a study treating patients with HCC and portal vein or inferior vena cava thrombosis with SBRT. Response rate was 36.6% and 39.0% for complete and partial response, respectively. Moreover, 76.7% of patients with elevated AFP levels before radiotherapy exhibited > 50% reduction of AFP levels within 3 mo after treatment. SBRT was proved effective and safe giving a median survival of 13 mo while maintaining a low toxicity profile, with grade 1 vomiting and nausea being the most common event.

Charged particle radiotherapy

More sophisticated techniques such as proton or carbon ion radiotherapy enable further dose escalation and precise dose delivery while maintaining a favorable toxicity profile. There are encouraging results from Tsukuba University's study treating patients unsuitable

for other treatment options with proton radiotherapy[91]. After a median follow-up of 318 patients for 19.3 mo, overall survival was 89.5% at 1 year and 44.6% at 2 years. Hepatic function, T classification, planning target volume and European Organization for Research and Treatment of Cancer performance status, were significant prognostic factors. Treatment related toxicity was minimal. There was no treatment discontinuation due to liver toxicity or treatment-related death.

The efficacy and safety of proton beam radiotherapy for peripherally located HCC, at least 2 cm away from the porta hepatis or gastrointestinal tract, was prospectively evaluated by Fukumitsu *et al*[92]. Fifty one patients received 66 Gy equivalents in 10 fractions. At 3 and 5 years OS was 49.2% and 38.7, respectively. None of the patients had tumor progression, while 29 had complete response and 10 a partial response. Despite a high local control rate of 94.5% at 3 years, 65% patients had a recurrence outside the irradiated field. Acute toxicity was minimal and no treatment-related liver failure was observed.

Proton and carbon ion therapy were comparable in terms of local control and survival in the series of Komatsu *et al*[93]. The study included 343 patients with tumors < than 15 cm. Two hundred and ten patients developed local recurrences in 3 years giving a 5-year local control rate of 90.2% for those receiving proton RT and 93% for those receiving carbon ion therapy. According to multivariate analysis, tumor size was an independent risk factor for local recurrence. For the whole series, 3-year OS was 59%.

Despite the favorable results of several studies of particle beam radiotherapy for HCC[94-97] we should keep in mind that proton and carbon ion radiotherapy is a quite expensive technique available in few facilities worldwide. Additionally, there is still room for photon radiotherapy (3DCRT, SBRT) for HCC patients. Dawson[98] suggests that photon RT is suitable for patients with CP. A liver function, and tumors that can be irradiated with sparing of the liver (tumors < 6 cm or at the dome of the diaphragm). Proton RT is advantageous mainly for patients with CP-B class liver function and tumor characteristics associated with higher liver doses after photon therapy (centrally located tumors > 8 cm). A dosimetric comparison of spot-scanning proton therapy *vs* intensity modulated radiation therapy suggests proton radiotherapy for HCC with nominal diameter > 6.3 cm with regard to radiation-induced liver toxicity[99].

Finally, neither photon or proton therapy is considered a suitable option for patients with CP-C liver function or diffuse, multifocal HCC.

3DCRT and hyperthermia

The full scope of the capabilities of radiation therapy is achieved particularly in combination settings with various anti-tumor modalities, the so-called multidisciplinary approach. To enhance the therapeutic efficacy of radiation sufficiently, one may choose radiation therapy in combination with hyperthermia treatment. Many studies concluded that local hyperthermia induced both direct and abscopal anti-tumor effects that might probably be the result of a systemic effect of hyperthermia in the host animal[100-102].

Lin *et al*[100] used nanosized Mn-Zn magnetic-fluid hyperthermia in combination with radiation therapy. The results, *in vivo* and *in vitro*, showed that the combination of magnetic fluid hyperthermia with Mn-Zn ferrite has better therapeutic effect than either of them alone. Zhang *et al*[101] used on extracorporeal HepG2 cells different temperatures, pressures of permeability and lengths of treatment time and they observed the killing effect on cell index. They concluded that the 46 ℃-distilled water-60 min achive to ideal killing effect on free cancer cells[101]. Linchun *et al*[102] showed that the toxicity after the combination of radiation therapy with hyperthermia was upper abdominal fullness, anorexia, nausea, vomiting, abdominal pain, marrow suppression. The combination is safe and effective in the treatment of hepatocellular carcinoma[102].

The logical inference from these researchs is that the abscopal effect is a desirable and common systemic reaction to localized cancer treatment. These data will encourage future therapeutic gain of hyperthermia in the treatment of hepatocellular carcinoma. The development of safer and reasonable therapies will be facilitated as we clarify the mechanisms for the abscopal effects. Future therapies will need to be optimized with tumor-type tailoring in consideration of various intra- or inter-tissue signals if these are to affect treatment outcome.

RADIATION INDUCED LIVER TOXICITY

Radiation delivery to liver lesions is limited by the tolerance of surrounding normal liver parenchyma. Hepatic radiation toxicity has for long been in the center of interest[103,104]. RILD has been defined as a clinical syndrome of anicteric hepatomegaly, ascites and elevated liver enzymes (particularly serum alkaline phosphatase) occurring from 2 wk to 4 mo after radiotherapy[105]. The underlying cause is a venoocclusive disease in the central portion of each lobe. Fibrous occlusion of central veins is the result of replacement by collagen of fibrin accumulated to endothelial cells of central veins after irradiation[106]. Dawson *et al*[105] have demonstrated a large volume effect for RILD. The mean liver dose is associated with the development of RILD with a threshold of 30 Gy with conventional fractionation. A mean liver dose of 31 Gy is associated with a 5% probability of RILD. This probability rises up to 50% for a mean dose of 43 Gy. These results are in line with the earlier work of Emami that defined the tolerance of normal tissue to therapeutic irradiation with an emphasis on partial volume effects[107].

Liver is a characteristic example of a radiobiologically parallel architecture model, with liver acini as functional subunits. The risk of developing a complication depends on dose distribution throughout the whole organ rather than the maximum dose to a small area. A complication

occurs if the fraction of liver damaged by RT exceeds the patients' functional reserve[108]. A high dose of RT can be delivered to a subvolume as long as the mean dose to normal parenchyma does not compromise its function. A dose as high as 100 Gy can safely be delivered to a small volume of normal liver (approximately 1/3 of whole liver) with a minimum or no risk of toxicity[105]. The Michigan group's study has shown that the tolerance of the liver is reduced in patients with primary liver cancer *vs* metastases. The mean liver dose associated with a 5% risk of RILD is 28 Gy at 2 Gy per fraction for primary liver cancer *vs* 32 Gy at conventional fractionation for metastatic live cancer[109].

In severe clinical cases, the RILD can lead to liver failure and death. Although many pharmacologic therapies have been tested in the past[103,110-112] there is still no standard therapy available for radiation-induced liver toxicity. Recently, new agents and strategies such as monoclonal antibodies against transforming growth factor-β[113] and transplantation of bone marrow-derived stem cells, adult hepatocytes or liver progenitor cells[114-116] have been tested in the treatment of liver disease. Their possible role in the setting of radiation-induced liver disease is still under investigation.

PALLIATIVE RADIOTHERAPY

For a long time, in terms of palliative setting, radiotherapy has been used for the treatment of distressing symptoms from HCC metastases. The lung, abdominal lymph nodes and the bones are the most common sites of extrahepatic metastatic HCC[117,118]. Unusual metastatic sites, such as central nervous system, have also been reported in the literature[119,120].

HCC lymph node metastases are sensitive to EBRT within a dose range of 8-60 Gy[121]. Sixty four per cent of patients subjected to RT with a dose 46-60 Gy achieved partial response and 18% a complete response[122]. In the series of Zeng *et al*[29], 50 Gy/25 fr was proven an effective palliative treatment for lymph node metastases, although survival decreases as the distance of lymph involvement from the liver increases, following the natural flow of lymph. The incidence of death resulting from lymph node-related complications was lower in the EBRT group in comparison to patients not receiving RT[29]. High rates (73% and 84%) of pain relief associated with HCC bone metastases have been reported in two series from South Korea and Japan, respectively[26,123].

Brain metastases are associated with extremely poor prognosis and median survival is 1-3 mo[120,124,125]. Increased survival is reported in patients that received aggressive treatment combing surgery and/or radiotherapy[120,124,125]. In the series of Han *et al*[126], patients treated with whole brain radiotherapy and/or gamma knife radiosurgery had a median survival time of 16 wk. Since brain metastases from HCC tend to bleed and rebleed after treatment, complete surgical resection should be attempted. However, decision for aggressive combination treatment is appropriate only for selected patients mainly without extra cranial tumor burden or viable liver disease.

Radiotherapy used with palliative intends is an effective and well tolerated treatment for common HCC metastases causing distressing symptoms.

CONCLUSION

The role of radiation therapy for hepatocellular carcinoma has evolved over the years. The technological advances that provided the means to deliver a tumoradical dose to liver lesions while sparing the surrounding normal parenchyma have given new insight to the treatment options for HCC. The literature supports the efficacy and safety of radiation therapy for HCC that has been for long considering a radioresistant tumor. Radiation therapies alone or in combination with other local therapies such as radiochemoembolization give encouraging results on local control and survival. We have successfully moved from the palliative role of radiotherapy for HCC to a new era of radiotherapy given as an effective treatment for patients not suitable for other therapeutic approaches.

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