Role of External Beam Radiation Therapy in Management of Hepatocellular Carcinoma

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Diagnosis at advanced disease stage and early vascular invasion are the bane of majority of patients with hepatocellular carcinoma (HCC) in India. The currently standardized curative and palliative treatment modalities [surgery, ablative techniques, trans-catheter chemotherapy, systemic chemotherapy] are suboptimal for a significant proportion of disease stages. Interest in radiotherapy for hepatocellular carcinoma has seen a resurgence with revolutionary improvements in targeting radiation doses safely. Encouraging results have been reported with a host of radiation techniques from conformal radiotherapy, stereotactic whole body radiation therapy to charged particle based therapies. The dissemination of this knowledge has been slow across other specialties involved in care of patients with HCC. However the increasing availability of radiotherapy services predicts a hopeful future for wider evaluation of radiotherapy in HCC. (J CLIN EXP HEPATOL 2014;4:S122-S125)

Cure with organ preservation is the ultimate aim of cancer treatment. Hepatocellular carcinoma occurs on chronically diseased livers making both cancer control and preservation of function essential for meaningful therapy.

Every living and dividing cell is susceptible to acute or delayed radiation induced damage depending on its metabolic status.¹ In modern oncology radiotherapy maintains pride of place for effective wide area tumor debulking and peri-operative sterilization due to increased susceptibility of dividing tumor cells compared to normal tissue; thereby inducing cell death by apoptosis. Its success is improving with the ability to effectively target higher doses while sparing surrounding vital structures.² The advanced loco-regional presentation and underlying liver disease limit the application of curative options such as liver transplantation or partial hepatectomy. The loco-regionally advanced presentation of HCCs presents an attractive opportunity for radiotherapy while the deep-seated location and co-existent liver disease in these patients continues to remain a challenge. Thus HCC is a radiosensitive tumor but inside a radiosensitive and mostly diseased liver. How-

ever revolutionary advances in targeting of radiation dose with conformal RT (CRT), stereotactic body RT (SBRT), image guided RT (IGRT) and charged particle RT are widening the role of radiotherapy in treating HCC.³

RADIATION TOLERANCE OF LIVER

The first report on the effect of radiation on liver documented the relative radio-resistance of normal hepatocytes and the occurrence of endothelial and bile duct damage at autopsy.⁴ The risk of radiation induced liver damage led to cautious under-dosing in initial reports of radiotherapy in HCC leading to their erroneous labeling as radio-resistant. In early trials involving the use of whole-liver RT, generally in combination with intra-arterial and/or intravenous chemotherapy, the reported 2-year survival rate was <10%.⁵ The whole-liver tolerance for radiotherapy (RT), with a 5% risk of radiation-induced liver disease (RILD) had been reported at whole-liver doses of 30-35 Gy in 2 Gy per fraction.⁶⁻⁸

The technical inability to deliver ablative doses without incurring a significant risk of radiation-induced liver disease (RILD) was another limitation. Radiation induced liver disease is identified by anicteric hepatomegaly, ascites, and elevated liver enzymes (alkaline phosphatase more than the transaminases) occurring typically between 2 weeks and 3 months after completion of RT.⁹ The primary site of radiation injury is the endothelium rather than the hepatocyte. Radiation-induced endothelial damage exposes the subendothelial basement membrane, leading to platelet activation and aggregation, and stimulation of dormant hepatic stellate cells. Fibrin thrombus causes venous occlusion, panlobular congestion, diffuse hemorrhagic and necrotic foci, and distention of hepatic

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Abbreviations: CRT: conformal radiotherapy; HCC: hepatocellular carcinoma; IGRT: image guided radiotherapy; RFA: radiofrequency ablation; RILD: radiation-induced liver disease; RT: radiotherapy; SBRT: stereotactic body radiotherapy

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sinusoids.¹⁰ Prolonged obstruction and activation of hepatic stellate cells results in hepatocyte loss and fibrosis. Radiologically, RILD presents with a “straight-border” sign, which is defined as any hepatic attenuation difference bordered by straight lines. RILD presents as demarcated areas of hypo- or hyperattenuation in a non-anatomic distribution, contrasting with vascular lesions.¹¹ No established therapies for classic RILD exist. Treatment of RILD is primarily supportive with a majority succumbing to liver failure.

Nonclassic RILD or radiation-associated liver dysfunction, typically occurs earlier (between 1 week and 3 months after therapy) and involves elevated liver transaminases more than five times the upper limit of normal or a decline in liver function (measured by a worsening of Child-Pugh score by 2 or more), in the absence of classic RILD. A confounder of RILD, especially in populations with pre-existing liver dysfunction, is the baseline rate of morbidity within this population due to their pre-existing liver disease including risk of hepatitis B flare.

In radiobiology the liver is considered a parallelly organized organ with independent functioning units. This parallel architecture allows the liver to tolerate substantial focal injury prior to any clinical sequelae. In noncirrhotic patients, surgical resection that leaves only a 20–25% liver remnant has been shown to be well tolerated.¹² Due to this redundant capacity, partial liver irradiation to high doses is possible if adequate normal liver parenchyma can be spared.

In reports of whole liver radiation upto 30–35 Gy in 2 Gy per fraction the RILD risk was 5%.^{13,14} Safe tolerance with partial radiation of liver upto 55Gy was initially reported by Ingold.⁵ Subsequent correlation analysis of radiation dose and liver volume correlation had concluded that doses in excess of 35 Gy should be limited to 30% of the liver when 18 Gy was delivered to the whole liver.¹⁵ The relation between dose and liver volume with risk of RILD is described statistically as a sigmoid curve. These curves when extrapolated, predict that the tolerance doses for one-third and two-thirds uniform partial liver irradiation associated with a 5% risk of RILD are 93 Gy and 47 Gy, respectively, for primary liver cancer (in 1.5 Gy twice a day).¹⁶ These projections have been validated in other reports.^{17,18}

The liver is one of the largest organs of the body; its triangular shape renders different adjacent organs such as the duodenum, colon, small bowels and kidney vulnerable depending on the liver segment involved leading to side-effects like nausea, vomiting, segmental colitis, renal damage and even radiation induced portal vein thrombosis.

The association between RILD and the volume of liver irradiated was overcome with improvement in radiation planning. To start with radiation planning was confined to two dimensions dependant on plain film X-rays lead-

ing to overdosage. Data for volume-based radiation dose-toxicity could not be obtained without the use of cross-sectional imaging in treatment planning. Use of computed tomography-based treatment planning resulted in more accurate definition of tumor volumes and radiation dose that the liver received. This led to re-drawing of the radiation dose-volume relationship of RILD and generated treatment planning parameters for safely treating liver tumors. Advances in “gating” of respiratory motion, immobilization, and image guidance during radiation treatments, have permitted further reduction of the planning target volume and correspondingly reduced the volume of normal liver irradiated. These have developed into stereotactic body radiotherapy (SBRT), a potentially ablative radiation strategy of high-dose radiation given in five or fewer fractions, for liver tumors.

Response assessment to radiotherapy is currently as per other therapies by mRECIST or EASL criteria, tumor response takes 2–3 months to detect and apart from shrinkage and loss of arterial enhancement has characteristic peritumoral increased enhancement in arterial and venous phases due to radiation induced peritumoral inflammation.¹⁹

CHARGED PARTICLE THERAPY

Compared to standard photon based radiotherapy which is absorbed exponentially across the tissue traversed; charged particle therapy [proton, carbon anion] deposits its energy predominantly at the end of the beam range. Towards the end energy is dissipated rapidly and the beam end leading to a sharp rise in energy called “Bragg’s peak”. This enables to prevent radiation damage in the tissue in the path of the beam and also to deliver a higher dose at the target. There is also less scatter of a proton beam compared to a photon beam. Also the terminal energy delivery of charged ions makes them safer in chronic liver disease where protecting the functioning liver reserve is paramount. As of now results with proton beam RT are better than all other forms.

The first reports on proton beam therapy for HCC reported in a series of 162 patients receiving hypofractionated (3.5–5) doses from 50 CGE to 84 CGE; 5-year local control rates of 86.9% and overall survival of 23.5%.²⁰ Majority of deaths were due to progressive liver disease. Majority of patients had asymptomatic rise in transaminases and actual radiation associated liver disease was seen in only 3%. Larger series corroborate local response rates of 90% with a 5-year survival upto 38%.²¹

Patients with portal vein invasion are currently offered sorafenib for reported survival benefits of 3–5 months. These patients with large tumors and compromised liver functions are suitable candidates for proton beam therapy. Local control rates upto 45% for 2 years have been

reported.²² Similarly encouraging responses with retreatment for recurrent or synchronous HCC have been reported with 5-year local control rate of 87.8% and 5-year overall survival rate of 56%.²³ A prospective phase II trial had reported preliminary results in 34 cases of unresectable HCC with 2-year local control of 75% and overall survival of 55% and no incidence of RILD.²⁴

Subsequent consolidated data for 76 patients showed median progression-free survival for the entire group was 36 months, with a 60% 3-year progression free survival in patients within the Milan criteria.²⁵ Among the 18 patients who were later transplanted complete pathological response was documented in 6; highlighting the curative potential of RT.

ROLE FOR RADIOTHERAPY

Fewer than 30% of patients are eligible for currently available curative treatments, namely liver transplant, surgery, and radiofrequency ablation (RFA), as a result of disease stage, poor liver function, or limited resources.^{26,27} Radiation represents a potentially ablative liver-directed therapy that is complementary to the existing options. Foreseeable roles for radiotherapy are:

- a. Difficult location: Tumor that is located in the dome of the liver, or near a major vascular structure (challenging for ablative techniques).
- b. Tumor vascular thrombus: In these patients unsuitable for TACE, sorafenib can increase 1-year survival, from 30% with best supportive care to 45%.^{28,29} Recent prospective reports document successful recanalization of thrombosed portal vein with stereotactic radiation therapy with 1-year survival rate of 55% and median survival of 17 months which are superior to sorafenib.³⁰ It is perhaps in high-risk patients that radiation may have its greatest benefit. Similar results have been reported with proton beam therapy [see vide supra].
- c. Bridge for liver transplant: There are successful reports of patients outside Milan's criteria being later transplanted after radiotherapy.^{25,31}
- d. Palliative therapy: Uniformly positive results have been documented with palliative intent RT.^{32,33} In an Indian study by Dhir et al 27 patients with HCC were treated by sequential methotrexate (75 mg/m²) and 5-fluorouracil (5-FU) (750 mg/m²) on day 1 followed on days 8–36 by external beam radiotherapy (total dose 30 cGy). The overall response to the treatment was 26%. More than a 50% reduction in serum AFP level was noted in 67% patients. Seventy-one percent of patients had palliation of pain following therapy. The median survival of responders was 11 months and of non-responders, 2 months.³⁴
- e. Combination therapies: Despite high local control rates with RT systemic recurrence remains the issue providing

valid rationale for combination with chemotherapy. There have been multiple reports previously suggesting synergism.³⁵ Studies evaluating concurrent chemotherapy or sequential TACE are underway.^{36,37}

To conclude adoption of radiotherapy as a standard care in treatment of hepatocellular carcinoma awaits data from prospective trials. Radiotherapy seems to be a promising option however, as of now it cannot be recommended outside trial settings.

CONFLICTS OF INTEREST

The author has none to declare.

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