

# Radiotherapy and hepatocellular carcinoma: update and review of the literature

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**Abstract.** – Historically radiotherapy has always played a limited role for the treatment of HCC due to the low tolerance of the liver and the subsequent risk of radiation induced liver disease (RILD). Technologist advancements in radiation planning and treatment delivery such as Stereotactic Body Radiotherapy (SBRT) combined with Image Guided Radiotherapy (IGRT) has allowed us to further increase tumor dose while maximally sparing the surrounding not involved liver.

Furthermore, together with the growing knowledge of radiobiological models in liver disease, several mono-institutional retrospective and prospective series are reporting very encouraging results. Therefore, radiotherapy might play a significant role for the treatment of unresectable HCC, alone or combined with other locoregional treatment such as transarterial chemoembolisation (TACE).

The rationale for studying this technique is really strong and it should be tested in well designed prospective randomized clinical trials.

## Key Words:

Hepatocellular carcinoma, Stereotactic body radiotherapy, Liver radiotherapy, Transarterial chemoembolization.

(BCLC)<sup>2</sup>, because it encloses both tumour characteristics (size and number of nodules) and medical data (patient's performance status, liver residual function and cancer related symptoms).

Based on the above staging system, therapeutic options are subdivided into radical curative treatments and palliative options. Patients affected by very early stage HCC or early stage are candidate to a radical curative treatment with 5 years overall survival of 100% and 50-75%, respectively. Instead, patients affected by Intermediate or Advanced Stage HCC are candidate to palliative treatments, mainly transarterial chemoembolisation (TACE). TACE is considered the standard of care in these patients on the basis of two published meta-analyses that cleared demonstrated 2 year overall survival benefit<sup>3,4</sup>. Recently a phase III randomized controlled trial has shown a 3 months survival improvement for advanced stage HCC with Sorafenib<sup>5</sup>. However, due to the poor prognosis for more advanced stages, enrolment in Phase II or Randomized Controlled Trials (RCT) testing new agents or techniques, is strongly recommended by international guidelines.

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer, most frequent primary tumour of the liver and the third cause of cancer related deaths following lung and stomach cancer worldwide<sup>1</sup>. HCC is a very heterogeneous disease and management of therapeutic approach may be variable and strongly related to patient's liver dysfunction as well as tumour stage. In clinical practice, the most commonly used staging system is Barcelona Clinical Liver Cancer

## *The Role of Radiation Therapy: Tridimensional Conformal Radiotherapy (3DCRT)*

Historically, the use of radiation therapy for the treatment of HCC has been limited by the poor tolerance of the whole liver to no more than 30-35Gy and subsequent high risk of developing radiation induced liver disease (RILD). RILD is a clinical syndrome characterized by an anicteric hepatomegaly, ascites and elevated liver enzymes (especially alkaline phosphatase), it may develop between 2 weeks to 4 months after hepatic irradi-

ation<sup>6</sup>. Early experiences of radiation therapy for advanced HCC date back to 1980, generally using low doses delivered to the whole liver combined with intra-arterial or intravenous chemotherapy and reporting 2 years overall survival rate less than 10% and a high rate of toxicity<sup>7</sup>. The advent of three dimensional conformal radiation therapy (3DCRT) has allowed both delivery of higher doses to limited volumes of liver yielding higher tumour control rate and reduction in irradiation of residual functional parenchyma in order to minimize toxicity.

Mornex et al<sup>8</sup> reported the results of a phase II French trial on 25 cirrhotic patients not suitable for curative therapeutic options with 1 nodule  $\leq$  5 cm or 2 nodules  $\leq$  3 cm, Child A (16 patients) or B (11 patients), who received 66Gy with conventional fractionation (2Gy/fraction; 30 total fractions) as unique treatment. Authors report a 92% overall response rate [80% CR (complete response) and 12% PR (partial response)], a 22% grade 4 toxicity developed only in Child B patients and a 22% "in field" and 41% "out field" recurrence rate. In Kim et al<sup>9</sup> experience 59 patients affected by advanced HCC with portal vein tumour thrombosis (PVTT), previously treated with a combination of TACE and radiofrequency ablation (RFA) (35 patients), Child A or B, ECOG (Eastern Cooperative Oncology Group) 0-2, underwent to a total dose range of 30-54Gy using 3DCRT and reported an overall response rate of 45,8%. Authors underline a significant relationship between radiation delivered dose and objective response rate (20% for RT dose  $<$  58 Gy10 and 54.6% for RT dose  $>$  58 Gy10) reporting 1 and 2 years survival rate of 40.7% and 20.7% respectively for responders, 25% and 4.7% respectively for non responders patients.

Considering the high rate of recurrences occurring within the liver but outside the high dose irradiated volume, the spatial cooperation synergism of TACE and 3DCRT has been widely tested in many trials.

In the Seong et al. trial<sup>10</sup> an heterogeneous population of 158 unresectable HCC (74% Child A and 26% Child B; 90% cirrhosis and 10% no cirrhosis; 51% PVT (portal vein thrombosis) and 49% no PVT; 75% tumour size  $<$  10 cm; 25% tumour size  $>$  10 cm) underwent local RT as primary consolidation treatment after TACE (107 patients) or as salvage after failure of repeated TACE (51 patients). After a mean follow up of 21.6 months the overall response rate was 67.1% and overall survival rate were respectively 59.4%,

30.5% and 9% at 1, 2 and 5 years. RT dose was the strongest prognostic factor for better survival both on an univariate and multivariate analysis.

Liu et al<sup>11</sup> reported results on 44 large unresectable HCC (6-25 cm) treated with RT (dose range 40-60Gy) showing a 61% of objective response rate and a survival rate at 1, 2 and 3 years of 60.5%, 40.3% and 32%. Overall, the majority of trials showed a significant benefit of RT combined with TACE in advanced stage HCC reporting 13% complete response rates, 25-78% partial response rates and an overall survival rates ranging from 10.2-53.8% at 2 years and 9-19% at 5 years<sup>12-14</sup>.

Moreover most of 3DCRT experiences reported a significant correlation between both the total dose delivered and the tumour response rate and between a baseline liver dysfunction and high grade toxicity effects. Above all patients Child B score are more likely to develop a radiation induced liver disease (RILD).

### ***The Role of Radiation Therapy: Stereotactic Body Radiotherapy (SBRT)***

Nowadays, the advancement in diagnostic imaging of HCC such as Contrast Enhancement Ultrasound (CEUS), four dimensional Computed Tomography (4DCT) scan or Magnetic Resonance (MRI) with gadolinium injection together with new therapeutic radiation technologies, such as Image Guided Radiotherapy (IGRT) and Stereotactic Body Radiotherapy (SBRT), has allowed further increases in tumour radiation doses while minimizing to surrounding normal tissues by a steep gradient dose to the periphery.

SBRT (Stereotactic Body Radiation Therapy) is a relatively new radiation technology providing very highly conformal potent ablative radiation dose with a rapid fall off gradient dose to well defined extracranial tumours (i.e liver) for a small numbers (1-5 fractions) of significantly large fraction size. The major advantage is the radiobiological efficacy of such high fraction dose on tumour tissues, the short treatment course with a limited number of fractions and the non invasive outpatient therapy. This technique is emerging as a new treatment modality and several single centre retrospective series have shown promising results (Table I).

In a study by Choi et al<sup>15</sup>, 20 patients with small HCC (3.8 cm average size) underwent SBRT (50Gy in 5-10 fractions). After a median follow up of 23 months they reported an overall response rate of 80% and 1 and 2 years overall

**Table I.** Stereotactic body radiotherapy for hepatocellular carcinoma.

Authors	Pts	CP class A (%)	Tumor size	Total dose number fractions	Response (%)	1 yr LC (%)	1 yr OS (%)	2 yr OS (%)	3 yr OS (%)	Toxicity ≥ G3
Choi et al <sup>15</sup> (R)	20	75	3.8 cm (mean)	50 Gy/ 5-10 fx	80	–	70	43	NA	0
Takeda et al <sup>16</sup> (R)	16	–	–	35-50 Gy/ 5-7 fx	75	100	100	100	–	0
Kwon et al <sup>17</sup> (R)	42	90	15.4 mL (range 3-82 mL)	30-39 Gy/3 fx	86	72	93	–	58.6	1
Seo et al <sup>18</sup> (R)	38	–	–	33-57 Gy/3-4 fx	–	79	68	–	–	–
Louis et al <sup>19</sup> (R)	25	88	1.8-10 cm	45 Gy/3 fx	–	95	79	–	–	1
Chan et al <sup>20</sup> (R)	16	–	–	45 Gy/10 fx	–	91	62	–	28	–
Mendez Romero <sup>21</sup> (P)	8	75	1.1-322 mL (22.2 mL)	37.5 Gy/3 fx 25-30 Gy/ 5-10 fx	–	75	75	40	–	18
Tse et al <sup>22</sup> (P)	31	100	9-1913 mL (173 mL)	24-54 Gy/ 6 fx	–	65	48	–	–	0
Andolino et al <sup>23</sup> (P)	60	60	3.1 cm (range 1-6.5 cm)	48 Gy/3 fx 40 Gy/5 fx	–	90	–	67	–	0

*Abbreviations:* CP: Child Pugh; Fx: fractions; LC: Local Control; OS: Overall Survival; R: Retrospective; P: Prospective.

survival rate of 70% and 43.1%, while no toxicity > G3 was observed. Takeda et al<sup>16</sup> reported a Japanese experience on 16 Child A or B solitary HCC previously treated with TACE (14/16 patients), who underwent to SBRT for a total dose of 35-50 Gy in 5-7 fractions. At a median follow up of 20.3 months a 75% overall response rate (50% complete response) and 100% overall survival was observed.

At the University of Korea Kwon et al<sup>17</sup> enrolled 42 HCC patients with good performance status (41/42 ECOG 0) and liver function (38/42 Child A), mainly pre-treated with TACE alone or combined with others locoregional therapies or surgery (36/42 patients) and no more eligible for radical treatment, to SBRT dose range 30-39 Gy in three fractions. Local progression free survival rate at 1 and 3 year was 72% and 68% respectively with a median progression free interval of 15.4 months. Overall survival rate at 1 and 3 year was 92.9% and 58.6% respectively while one patient experienced fatal late toxicity (grade 4). In the multivariate analysis the strongest factors associated with poor survival resulted greater tumour volume (> 32 cc) and distant metastases occurrence. Seo et al (18) treated 38 patients with HCC at dose range 33 to 57 Gy in 3 to 4 fractions. With a median follow up of 15 months,

79% local control and 68% overall survival was found.

Louis et al group<sup>19</sup> reported their case load of 25 patients with HCC (tumor size 1.8-10 cm), especially Child A (88%) undergone to 45Gy in 3 fractions. The 1 year local control and overall survival rate was 95% and 79% respectively and 1 patient developed a grade 3 non haematological toxicity (duodenal ulcer).

The retrospective single centre review by Chan et al<sup>20</sup> on 16 advanced HCC treated with SBRT at 4.5 Gy for 10 fractions reported an overall control rate of 91%, a median overall survival of 23 months and 1 and 3 year overall survival rate of 62% and 28% respectively.

Mendez Romero<sup>21</sup> treated 11 HCC lesions in eight patients delivering 37.5 Gy in 3 fractions to patients without cirrhosis or nodule size <4 cm with cirrhosis and 25-30 Gy in 5-10 fractions to nodule size ≥ 4 cm or HCC with associated cirrhosis. The 1 year local control and overall survival rate were both 75% and a higher rate of toxicity > G3 was observed in Child B patients (18% RILD). All failures occurred in the 25 Gy group.

Tse et al by the University of Michigan group<sup>22</sup> reported their experience on 31 Child A large unresectable HCC who underwent to SBRT

for a total dose of 24-54 Gy (median dose 36 Gy) in 6 fractions. Almost half of the patients had portal vein tumour thrombosis (PVTT). The median survival was 11.7 months (11.6 months for patients with PVTT and 17.2 months for patients with no PVTT) and 1 year local control and overall survival rate was 65% and 48% respectively, while no treatment related toxicity  $\geq$  G3 was observed.

Recently, the latest update of the largest phase I study of SBRT on HCC at the Indiana University Simon Cancer Center (IUSCC) has been published<sup>23</sup>. Sixty with liver-confined HCC received SBRT at a total dose of 48 Gy in 3 fractions (36/60 patients with Child A) and 40 Gy in 5 fractions (24/60 patients with CTP B); the medium tumour size was 3.1 cm (range 1-6.5 cm) with a maximum number of lesions  $\leq$  3. The reported median Progression Free Survival (PFS) and Overall Survival (OS) were respectively 20,4 months and 44.4 months while the actuarial 2 year LC, PFS and OS were 90%, 48% and 67% respectively. Once again, Authors outlined the strongest correlation of OS with larger tumour volume, poor liver function (Child Class B) and lower delivered doses as well as absence of orthotopic liver transplant. No  $\geq$  Grade 3 toxicities occurred but an increase in Child class within 3 months after treatment was observed.

## Discussion

According to the American Association for the Study of Liver Diseases (AASLD) Practice Guideline for the management of HCC, surgery, orthotopic liver transplantation and RFA (Radiofrequency Ablation) are the main options for curative treatment of HCC. Unfortunately only 30-40% of new diagnosed HCC are suitable for radical treatments and the majority of patients are candidates only to “non curative” locoregional or systemic therapies. In this set of patients, TACE is the first line treatment that has shown better survival results compared with symptomatic therapy alone, reporting a survival rate ranging from 31 to 63% at 2 years and a 35% objective responses rate<sup>24,25</sup>.

The role of external beam radiotherapy has always been limited by the low dose tolerance of liver to radiation and subsequent high risk of RILD. Latest technological developments in RT planning and treatment delivery has suggested a significant benefit for patients affected by “inter-

mediate” or “advanced” HCC, alone or combined with TACE, in order to improve clinical results. Better results have been achieved after enrolling limited sized and number lesions, while cases of serious toxicity have been observed only in Child B patients. Several mono-institutional experiences have shown promising results with a high rate of complete (50-60%) and objective responses (75-80%), as well as low rate of severe toxicity.

Despite the heterogeneity of selected patient population, SBRT seem to provide a higher rate of complete and overall responses. Tumour volume size and residual liver function have shown to be the strongest predictive factors limiting the total dose to the HCC nodule and consequently the clinical results. Furthermore, SBRT could be used in HIV-infected HCC patients, when a significantly shorter survival time is demonstrated<sup>26,27</sup>, although it is possible an aggressive management<sup>28-31</sup>.

After SBRT, the main cause of progression disease is related to “out field” recurrence, globally, this support a strong clinical rationale of combining RT with TACE for both a local and regional effect. Instead, if a portal vein tumour thrombosis (PVTT) occurred, TACE has a lack of efficacy because it is associated with a high risk of ischemic liver insufficiency and mortality. Despite few literature, SBRT might be a valid choice as symptoms palliation in HCC patients with portal vein tumour thrombosis.

HCC patients, correctly stratified, should be allowed and encouraged to participate in clinical studies using SBRT and/or Radiotherapy with or without TACE.

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