



Applicability and Potentiality of Stereotactic Body Radiotherapy in Management of Hepatocellular Carcinoma



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Introduction

Hepatocellular carcinoma (HCC) represents 80 to 90 percent of primary liver malignancy. It is the fifth most common cancer in the world, and the third most common cause of cancer related death, so it is considered as a major health problem worldwide [1]. Non-surgical strategies for tumor ablation as transarterial chemoembolization (TACE), radiation therapy, and radioembolization are alternatives for patients who are not candidates for surgical resection or liver transplantation, and whose tumor is either too large or multifocal for a local ablation [2].

Aim of the Work

The aim of this work is

- First: To evaluate the response of the tumor to radiotherapy in patients with Barcelona Clinic Liver Cancer (BCLC) stage A, B, and C of HCC based on modified Response Evaluation Criteria In Solid Tumor (mRECIST).
- Second: To assess Stereotactic Body Radiotherapy (SBRT) associated toxicity to National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE).
- Third: To determine the rate of local progression, progression free survival (PFS) and overall survival (OS) all at baseline and 1 month, 3 and 6 months after SBRT treatment.

Patients and Methods

To achieve these goals, this study was conducted on 47 patients diagnosed with HCC in the period between June 2014 and June 2015 that presented to the Department of Radiation Oncology, University of Michigan, United States of America. The enrolled patients had confirmed HCC who were not candidates for surgical resection, while TACE done prior to study enrollment is allowed if there were no more than 3 procedures within 18 week period and SBRT can begin within 6 weeks of the last TACE

procedure. The enrolled patients were at the age > 18 years old, with Child-Pugh class A or B, performance status (ECOG PS)=0, 1 or 2, albumin >2.4g/dL, total bilirubin <3mg/dL, INR <1.5, creatinine <2.0mg/dL, AST or ALT <6 times upper range of normal.

Linear accelerator based SBRT technique was done with the use of 3-dimensional conformal technique (3DCRT), intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT). Patients were treated with either three or five fractions using 8-13Gy per fraction delivered 2-3 times per week with total dose range from 17-60Gy delivered to a highly focused target volume of HCC lesion.

Patients were followed up every day during radiotherapy; then one month after treatment by physical examination, laboratory investigations and triphasic CT was done after 1 month, 3, 6 and 1 year to detect patient's response to SBRT using mRECIST, laboratory investigations to evaluate the toxicity of SBRT, local control, PFS, and the OS were reported and registered for each patient.

Results

The radiological target lesion response to SBRT based on mRECIST criteria was reported at 1 month, 3, 6, and 12 months. We did not report any patient with progressive disease during the follow up period. After 1 year, there were 5 patients (6 lesions) with complete response, 4 patients (4 lesions) with partial response, 3 patients (5 lesions) with standard disease. When analyzing different factors and its correlation with target lesion response. We found that alpha fetoprotein (AFP) level at baseline is significantly correlated with the degree of target lesion response ($p=0.012$). When correlate the pre-treatment BCLC class is significantly correlated with the degree of target lesion response ($p=0.005$). Regarding factors affecting overall survival; we found significant correlation between overall survival and

pre-treatment Child-Pugh score and BCLC classification ($p=0.01$ and 0.03) respectively.

As expected the total SBRT dose is significantly correlated with the overall survival ($p=0.05$) and we found high significant correlation between mean dose to PTV and mean dose to GTV ($p=0.0009$ and 0.001) respectively, which means that increasing the dose leads to better response hence to better overall survival.

With forward selection of the significant prognostic factors for OS using the data from the univariate analysis to run a multivariate model, we found that the BCLC in early stage at baseline decreases the hazard of death by 75% when adjusting for mean dose to GTV.

Regarding factors affecting PFS; there was a significant correlation between progression free survival and pre-treatment Child-Pugh score ($p=0.03$). There are also significant correlation between PFS and the type of treatment received before SBRT, especially in patients of TACE and theraspheres ($p=0.05$ and 0.001) respectively. After 6 months grade 3 toxicity were observed in 19 patients (40.4%); these complications include worsening ascites ($n=3$), laboratory analysis disturbance ($n=16$). Significant grade 4 toxicity observed in only one patient as extremely low sodium level. No deaths were seen as a consequence of SBRT-induced complications. Our results were almost consistent with results reported from other studies done by Yamashita, Culleton & Scoretti M [3-5].

Conclusion

Stereotactic body radiotherapy (SBRT) is a non- invasive and highly effective in improving survival rate and provides

excellent local control of HCC with minimal toxicity. SBRT has a good indication for whom other local treatment options are hardly available or contraindicated as in patients with medical co-morbidities such as marked thrombocytopenia, inoperable patients or lesions that are difficult to reach or poorly visualized by ultrasound or in a close proximity to a major vessel, gallbladder, gastro intestinal tract with potential for perforation. Factors influencing the survival and local control of the tumor in our study are pre-treatment Child-Pugh stage and BCLC classification and the SBRT dose. Late scores at presentation affect negatively the survival rate.

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