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Three-dimensional conformal radiotherapy to hepatocellular carcinoma associated portal vein tumor thrombosis: Safety profile and toxicity

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ABSTRACT

In this study we aimed to determine safety profile and acute side effects of three-dimensional conformal radiotherapy (3DCRT) to portal vein tumor thrombus (PVTT) in cases of hepatocellular carcinoma (HCC). Thirty four consecutive patients were enrolled from Jan 2018 till Feb 2020; thirty of them fulfilled criteria for final analysis. Patients received 45Gy in 25 fractions to planning target volume (PTV). The median overall survival of the studied patients was 8.0 months. Responders had significant longer survival than non-responders (12 and 6 months respectively). No treatment related Grade 4 - 5 toxicity was observed. Only one patient (3.3 %) developed grade 3 elevation of bilirubin. Grade 1 nausea/vomiting were the most common side effect, it occurred in 22 patients (73.3%). Patients who didn't develop liver enzymes elevation, leukopenia or thrombocytopenia had better response and survival than patients who developed higher grades of toxicity. In addition to its survival benefit; 3DCRT to PVTT in cases of HCC is well tolerated with favorable toxicity profile.

Keywords: Hepatocellular Carcinoma, Portal Vein Thrombosis, 3D Conformal Radiotherapy, Safety, Toxicity

1. INTRODUCTION

HCC is a global health problem. In 2020, liver cancer in men ranks the fifth commonest cancer, the ninth in women and represents the third commonest cause of death due to cancer worldwide. In Egypt liver cancer in men ranks the first in prevalence among other cancers and the second in women (Sung et al., 2020). Treatment strategies of HCC vary according to disease stage, underlying liver condition and patient performance status. According to staging and treatment options of Barcelona Clinic Liver Cancer (BCLC) patients with early stage disease, good liver condition and good performance are candidates for surgical resection. Patient with early stage disease which fit

into Milan criteria can have liver transplantation with 5 years survival rate of 70% (Llovet et al., 2021). Patients who are unfit for surgery can undergo local ablative techniques with curative intent (Putzer et al., 2020).

Patients having good liver function, good performance and intermediate stage HCC are candidates of transarterial chemoembolization (TACE), transarterial radioembolization (TARE) (Llovet et al., 2021). Patients with advanced stage, good performance and good liver function are candidates for systemic therapies as Sorafenib, Regorafenib, Lenvatinib, Ramucirumab, Cabozantinib and immunotherapy as Nivolumab, Pembrolizumab or combinations as Nivolumab -Ipilimumab combination and Atezolizumab - Bevacizumab combination (Llovet et al., 2021). Patients with vascular invasion have poor prognosis and are usually treated as advanced HCC as there are no specific current guidelines for these cases (Kawagishi, 2020).

Historically radiation therapy (RT) had limited role in HCC treatment due to Radiation Induced Liver Disease (RILD) hazards (Dawson and Ten, 2005), however advances of radiation therapy allowed delivery of high doses of radiation to target while sparing normal tissues. RT is now used as local ablative method for early stage HCC in the form of stereotactic body radiation therapy (SBRT) with high local control rates (Rim et al., 2019). Recently many trials evaluated the role of external beam radiotherapy (EBRT) in cases of HCC with macrovascular invasion as PVTT with doses ranging from 30–71.8 Gy in 1.8–6 Gy per daily fraction either alone or combined with TACE or concurrent chemotherapy. Rate of objective response was around 43% to 74%, and overall survival rate at 1 year ranged from 45% to 86% and at 2 years ranged from 23% to 69%. About 0–13% of cases developed grade 3 hepatotoxicity and was more pronounced in combined modality treatment (Chen, 2019).

2. METHODS

We enrolled thirty four patients diagnosed with hepatocellular carcinoma and tumor thrombus in the portal vein in this prospective single arm study from January 2018 to February 2020. The inclusion criteria included: 1- Patients with clinical diagnosis of HCC according to American Association for the Study of Liver Disease (AASLD) guidelines (Forner et al., 2018). 2- Tumor thrombus diagnosed by contrast-enhanced computed tomography (CT) as intraluminal filling defect lesion. 3- Patients with Child-Pugh classification A or B ≤7. 4- Patients with performance status of 0-2 according to Eastern Cooperative Oncology Group. The exclusion criteria included: 1) Performance status (3- 4). 2) Child-Pugh class B>7, class C. 3) Presence of extrahepatic metastasis. Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript. The study was approved by the Medical Ethics Committee of Zagazig University Faculty of Medicine (ethical approval code: 4613/2018) approved the research.

Radiation therapy

Patients were simulated in supine position with both arms raised above the head. CT planning for RT was done under free breathing conditions. Medial and lateral tattoos were done at the site of reference points which were marked with radiopaque markers during CT scan. Multi-slice CT with 2.5 mm slide thickness was done. Gross tumor volume (GTV) was defined as a hypo dense filling defect of the portal vein and if primary tumor was close to the thrombus, inclusion of primary tumor in to GTV was considered. Clinical target volume (CTV) was 1cm margin from the GTV. Planning target volume (PTV) of a 1–2 cm margin from the CTV was given to include daily set-up variation and respiratory movement. Plan acceptance was according to the following constraints: 1) PTV covered by at least 95% of the prescribed dose; 2) Maximum accepted dose for hot spots within the PTV was 107% of the prescribed dose; 3) Volume of liver receiving 25 Gy (V25) <50%. 4) The mean liver dose <30 Gy. 5) The maximal spinal cord dose <45 Gy. 6) The mean dose to both kidneys <20 Gy. The prescribed dose was 45Gy in 25 fractions. 5 fractions per week each is 1.8 Gy. Multiple fields were used using multi-energy linear accelerator.

Treatment Evaluation and Follow up

Patients were monitored weekly by physical examination, complete blood counts and liver enzymes. One month after end of RT CT chest, abdomen and pelvis with contrast and serum AFP were done for assessing treatment response, and then follow up by CT every 2-3 months for 1 year. The response of the PVTT to treatment was assessed based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (Therasse et al., 2000), Patients were classified into 2 groups: A- Responders: complete response (CR) and partial response (PR). B- Non-responders: stable disease (SD) and progressive disease (PD). Evaluation of toxicity was done based on Common Terminology Criteria for Adverse Events (CTCAE), ver. 4.03.

Statistical analysis

Chi-square test or Fisher's exact test was used to evaluate relationship between PVTT response and other variables. We used Kaplan-Meier method in estimating overall survival which was measured from diagnosis date to death or last follow up date. For univariate survival analyses, we used log-rank test in evaluating differences.We performed statistical analysis by SPSS version 25 (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). P-value < 0.05 was considered statistically significant.

3. RESULTS

Mean age of the studied patients was 56.7, their age ranged from 48 to 68 years. 13.3% were females and 86.7% were males. 24 patients were class A according to Child-Pugh. 63.3% of patients had ECOG performance status 1 (Table 1). 10% of patients had tumor size <2cm while 60% had tumor size >5cm. 16.7% of patients had abdominal lymph node metastasis. 23.3% of patients had thrombus size <3cm. Patients who had tumor thrombus in portal vein, portal vein branch, both were 33%,6.7% and 60% respectively. CR, PR, SD and PD occurred in 0%, 36.7%, 50% and 13.3% of patients respectively (Table 2).

Table 1 Clinical and laboratory characteristics of the studied patients

Variables	Study patients (n=30)
Child-Pugh, n (%):	
A	24 (80.0%)
B	6 (20.0%)
Total bilirubin, n (%):	
<2	24 (80.0%)
2-3	5 (16.7%)
>3	1 (3.3%)
Serum albumin, n (%):	
>3.5	21 (70.0%)
2.8-3.5	8 (26.7%)
<2.8	1 (3.3%)
INR, n (%):	
<1.7	28 (93.3%)
1.7-2.3	2 (6.7%)
Performance status, n (%):	
0	3 (10.0%)
1	19 (63.3%)
2	8 (26.7%)

Table 2 Tumor characteristics of the studied patients.

Variables	Study patients (n=30)
Tumor size, n (%):	
<2cm	3 (10.0%)
2-5cm	9 (30.0%)
>5cm	18 (60.0%)
Abdominal lymph node metastasis, n (%):	
Yes	5 (16.7%)
No	25 (83.3%)
Thrombus size, n (%):	
<3cm	7 (23.3%)
≥3cm	23 (76.7%)
Thrombus location, n (%):	
Portal vein	10 (33.3%)
Portal vein branch	2 (6.7%)

Both	18 (60.0%)
The response, n (%):	
CR	0 (0.0%)
PR	11 (36.7%)
SD	15 (50%)
PD	4 (13.3%)

Median overall survival was 8 months and survival at one year was 32.1%. Regarding acute toxicity; only 1 patient developed grade 3 elevation of serum bilirubin. 73.3% developed grade 1 nausea and vomiting, 26.7% developed grade 1 liver enzymes elevation. 20.0% of patients developed grade 1 anemia, 30% developed grade 1 leukopenia and 33.3% developed grade1 thrombocytopenia (Table 3). Correlation between response and grades of toxicity was done and it showed that response was associated with low grade toxicity in liver enzymes, leukocytes, and platelets (Table 4). Survival was associated with lower grade elevation in liver enzymes, serum bilirubin and lower grade leukopenia and thrombocytopenia Figure (1).

Table 3 Acute toxicity in the studied patients:

Variables	Study patients (n=30)
Nausea & vomiting grade, n (%):	
0	5 (16.7%)
1	22 (73.3%)
2	3 (10.0%)
3-5	0 (0.0%)
Liver enzymes grade, n (%):	
0	18 (60.0%)
1	8 (26.7%)
2	4 (13.3%)
3-5	0 (0.0%)
Anemia, n (%):	
0	24 (80.0%)
1	6 (20.0%)
2	0 (0.0%)
3-5	0 (0.0%)
Bilirubin grade, n (%):	
0	23 (76.7%)
1	5 (16.7%)
2	1 (3.3%)
3-5	1 (3.3%)
Leukocytes grade, n (%):	
0	18 (60.0%)
1	9 (30.0%)
2	3 (10.0%)
3	0 (0.0%)
4-5	0 (0.0%)
Platelets grade, n (%):	
0	18 (60.0%)
1	10 (33.3%)
2	2 (6.7%)
3	0 (0.0%)
4-5	0 (0.0%)

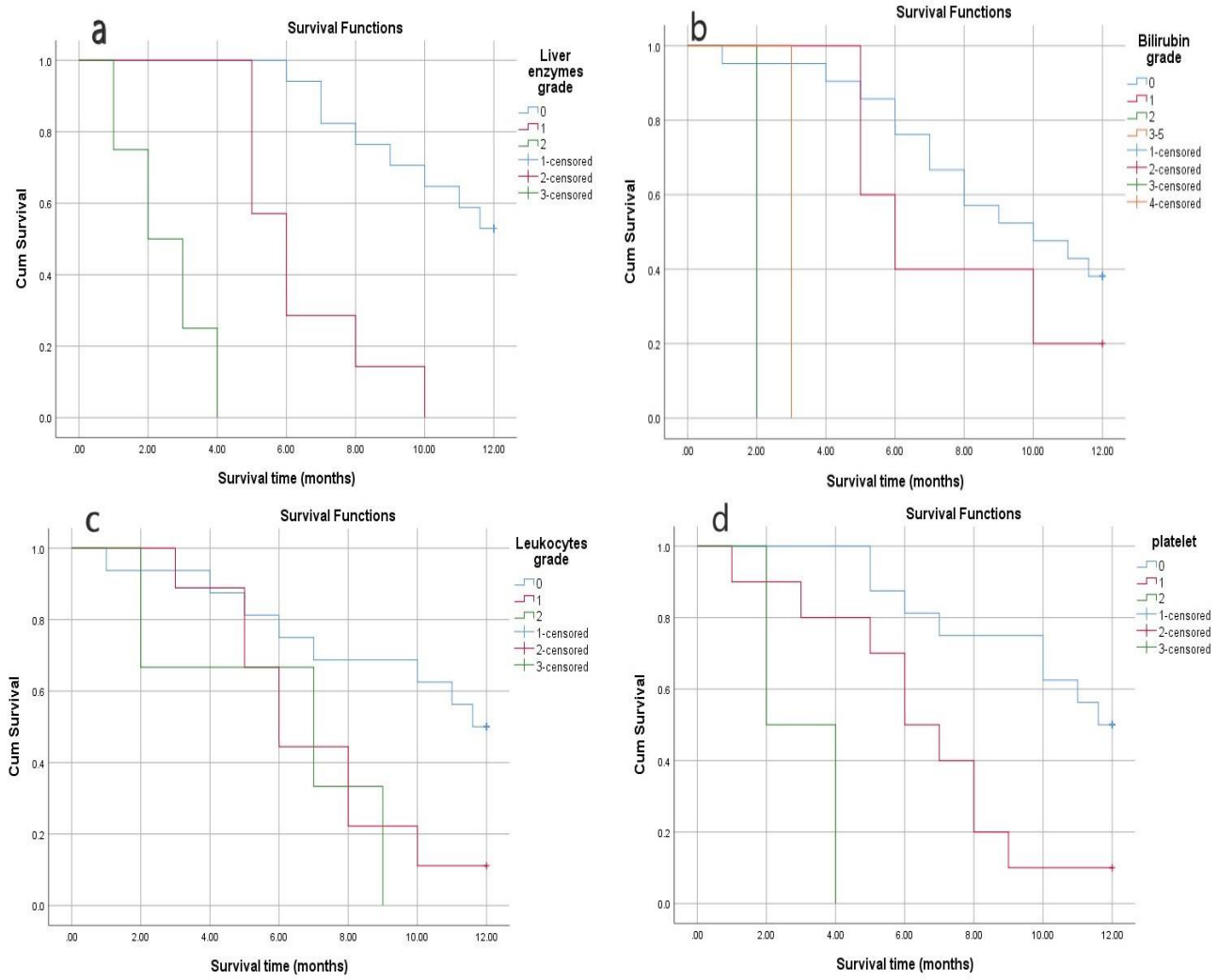

Figure 1 Survivalaccording to: a) liver enzymes grade, b) grade of serum bilirubin, c) grade of leukopenia, d) thrombocytopenia grade.

Table 4 Association between response and acute toxicity in the studied patients

Variables	Responders (n=11)	Non-responders (n=19)	Test of sig.	P
Nausea & vomiting grade, n (%): 0 (n=5) 1 (n=22) 2 (n=3)	 3 (60.0%) 7 (31.8%) 1 (33.3%)	 2 (40.0%) 15 (68.2%) 2 (66.7%)	 χ^2 1.7	 0.2
Liver enzymes grade, n (%): 0 (n=18) 1 (n=8) 2 (n=4)	 10 (55.6%) 1 (12.5%) 0 (0.0%)	 8 (44.4%) 7 (87.5%) 4 (100%)	 χ^2 7.1	 0.005 S
Anemia, n (%): 0 (n=24) 1 (n=6)	 9 (37.5%) 2 (33.3%)	 15 (62.5%) 4 (66.7%)	 fisher	 0.9
Bilirubin grade, n (%): 0 (n=23) 1 (n=5) 2 (n=1)	 9 (39.1%) 2 (40.0%) 0 (0.0%)	 14 (60.9%) 3 (60.0%) 1 (100%)	 χ^2 1.2	 0.7

3-5 (n=1)	0 (0.0%)	1 (100%)		
Leukocytes grades, n (%): 0 (n=18) 1 (n=9) 2 (n=3)	 9 (50.0%) 2 (22.2%) 0 (0.0%)	 9 (50.0%) 7 (77.8%) 3 (100%)	χ^2 4.9	0.03 S
Platelets grades, n (%): 0 (n=18) 1 (n=10) 2 (n=2)	 10 (55.6%) 1 (10.0%) 0 (0.0%)	 8 (44.4%) 9 (90.0%) 2 (100%)	χ^2 7.7	0.005 S

4. DISCUSSION

Hepatocellular carcinoma accompanied with vascular invasion is known to have poor prognosis. According to Barcelona Clinic Liver Cancer staging system (BCLC), HCC with vascular invasion is considered advanced disease and the treatment option is systemic therapy which is the treatment option for cases with extrahepatic spread (Kawagishi, 2020). Several investigators evaluated the role of surgery as treatment option for cases of HCC with vascular invasion (Pawlik et al., 2005). High rates of rapid disease recurrence and high risk of liver cell failure made this approach only suitable for very highly selected cases (Kawagishi, 2020). PVTT is a contraindication to TACE as it may lead to liver cell failure due to ischemia (Kim et al., 2009) but still can be done in highly selected cases with very good liver functions and collateral circulation (Zhang et al., 2017). Liver is radiosensitive organ, whole liver has low radiation tolerance (Minagawa and Makuuchi, 2006) but with advances in RT and development of 3DCRT, Intensity modulated radiation therapy (IMRT) and SBRT; RT became a treatment option for HCC cases either as a local ablative option for early stage liver tumors or for PVTT with good efficacy and minimal toxicity (Rim et al., 2019; Gabal et al., 2017).

We conducted this study to evaluate efficacy and safety of 3DCRT in treatment of HCC associated PVTT. Grade 1nausea and vomiting was the most frequent side effect (73.3%), only one patient had grade 3 elevation of bilirubin. Grade 1 liver enzymes elevation occurred in eight patients only. Grade 1 anemia occurred in six patients while grade 1 leukopenia and grade 1 thrombocytopenia occurred in nine and ten patients respectively. Our safety data are going with the study done by Rim et al., (2012) in which RT dose to the PTV ranged from 38 to 65 Gy in 1.8-2.5 Gy per fraction there were no grade 3 toxicity; 6.7% of patients had grade 2 nausea, 13.3% had grade 2 abdominal pain and 4.4% had grade 2 duodenal ulcer.

Tang et al., (2013) conducted a study in which RT dose to the PTV ranged from 30 to 52 Gy in 3-4 Gy per fraction. He reported loss of appetite and nausea as the most frequent side effect while Alanine transaminase elevation, myelosupression, gastrointestinal bleeding occurred in 8.1%, 35.1%, 3.2% of patients respectively. Nakazawa et al., (2014) also didn't report any grade 3 GI toxicity, regarding hematological toxicity; grade 3 leucocytopenia was observed in 1 patient in the RT group in which patients received 50 Gy to PTV in 2Gy per fraction. Median survival in our study was 8 months. Responders had statistically significant prolongation in survival compared to non- responders (12 months and 6 months respectively, p=0.001) which was the same in studies conducted by Rim et al., (2012), Huang et al., (2009) and Gabal et al., (2017). We studied relationship between response, survival and grades of toxicity and we found that patients who didn't experience elevation in liver enzymes or leukopenia or thrombocytopenia during RT had statistically significant higher response rates and survival.

5. CONCLUSION

3DCRT to HCC associated PVTT is safe and effective therapeutic option, lower grades of toxicity during treatment are associated with better response rates and survival.

Conflict of interest

The authors declare that there are no conflicts of interests

Funding

This study has not received any external funding

Informed Consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of Faculty of Medicine Zagazig University (ethical approval code: 4613/2018) approved the research.

Author's Contribution

AG, RS, AF, AM contributed to the conception and design of the study. RS, AG conducted data analysis. AG drafted the manuscript and was a major contributor in writing the manuscript. The manuscript was critically revised by RS, AF and AM. All authors read and approved the final manuscript.

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Data and materials availability

All data associated with this study are present in the paper.

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