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# Radiation Induced Liver Damage in Patients with Liver Cancer

SARAH A. NASSAR, M.Sc.*; IMAN ABD ELHADY, M.D.*; ASHRAF MOUNIR, M.D.* and MAHA KAMALELDIN, M.D.*

*The Departments of Clinical Oncology* and Physics Radiation Oncology**, Faculty of Medicine, Cairo University*

## Abstract

*Background:* Assessment of toxicity of radiation therapy and factors that influence the occurance of toxicity in patients with inoperable Hepatocellular carcinoma

*Aim of Work:* To evaluate the safety of radiation therapy using volumetric modulated arc therapy in patients with inoperable Hepatocellular carcinoma.

*Patients and Methods:* Between May 2014 and April 2016, twenty five patients with inoperable Hepatocellular carcinoma and not amenable to local ablative therapies received radiation therapy using VMAT 50.4 Gy in 28 fractions. We evaluated clinical as well as dosimetric factors related to the occurrence of RILD.

*Results:* RILD occurred in 28% of the patients and the mean volume of PTV was the only factor causing statistically significant difference in the occurrence of RILD with a mean PTV volume of 620.2cc in the RILD group versus 579.7cc in the No RILD group with a $p$=0.028

*Conclusion:* Lowering PTV volume contributes in the prevention of occurrence of RILD.

***Key Words:*** *Hepatocellular carcinoma – Volumetric modulated arc therapy – Radiation induced liver damage.*

## Introduction

**HEPATOCELLULAR** carcinoma (HCC) is the fifth most common malignancy and the third most common cause of cancer-related death in the world [1].

According to the results of national population based registry program of Egypt 2008-2011 Hepatocellular carcinoma is the most common prevalent cancer in males accounting for 33%, preceding bladder (10.7%), lung (6%) and prostate (4.2%).

***Correspondence to:*** Dr. Sarah A. Nassar,
The Department of Clinical Oncology, Faculty of Medicine, Cairo University

Surgery, provides survival rates 70% at 5 years, is appropriate in a small fraction of patients because of advanced stage at diagnosis [2].

Patients also can be treated with Trans Arterial Chemo Embolization (TACE), Radio Frequency Ablation (RFA), Percutaneous Ethanol Injection (PEI), and Targeted Agents. All these agents are used in early stages HCC, and restricted to specific locations in the liver, and requires high cost and presence of co morbidities [3].

Radiotherapy is an option for this type of patients but it was limited by low tolerance dose of liver and occurrence radiation induced liver disease (RILD). A clinical syndrome characterized by ascites, anicteric hepatomegaly, and impaired liver function, usually occurs 2 weeks to 4 months after completion of Radiotherapy.

It is affected by total dose to the liver and volume of irradiated normal liver. RILD is treated by supportive measures. In severe cases of RILD, hepatic failure may occur. The low tolerance dose of the liver limits the application of higher radiation doses to the tumor [4].

New techniques in radiotherapy have allowed higher doses to target the tumor while limiting the dose to normal liver tissue.

More conformal types of radiotherapy have been developed to deliver highly conformal treatment with minimal damage to surrounding normal liver, including IMRT, IGRT, and SBRT.

The availability of intensity modulated radiotherapy (IMRT) and the evolution of volumetric modulated arc therapy (VMAT) was a breakthrough in treatment of HCC patients. VMAT was formally used in metastatic liver lesions but then its use is extended to primary HCC.

*The role of VMAT became more obvious in treatment of HCC based on many studies:*

- Verbakel WF et al., and Wagner et al., compared Rapid Arc with IMRT for different malignancies and concluded that the major advantages of Rapid Arc over IMRT were the lower MUs and the shorter treatment time, which reduces the intrafractional movement [5,6].
- Park et al., study, treated advanced HCC patients with PVTT, both V30 and dose to organs at risk were lower in Rapid Arc compared to IMRT [7].
- Wang et al., reported that Rapid Arc in treatment of advanced HCC patients not amenable to surgery or local therapies yielded overall survival and local control benefit which makes it appropriate technique for management of these patients.

*Aim of work:*

The aim of this study is to evaluate the safety of radiation therapy using volumetric modulated arc therapy in patients with inoperable Hepatocellular carcinoma and not candidates for local ablative therapies and to evaluate clinical and dosimetric factors related to the occurrence of RILD.

## Patients and Methods

The study was carried out at Kasr El Aini Center of Clinical Oncology (NEMROCK) after acceptance of our scientific and ethical committees and a written consent from all patients before their recruitment in the study.

Twenty five patients with radiologically or pathologically proven HCC were assigned to receive Rapid Arc technique with radiation dose of 50.4Gy given in conventional fractionation of 1.8Gy/fraction in 28 day duration.

*Pretreatment evaluation:*

*Includes:*

- Radiologically or pathologically proven HCC.
- Tumor medically inoperable or technically unresectable (vascular invasion, more than 5cm, 3 nodules more than 3 cm).
- Tumor not amenable to TACE(Portal vein thrombosis or presence of arterio-portal fistula).
- Tumor not amenable to RFA (Tumors larger than 5cm; Unsafe location relative to visceral organs, bile ducts & vessels or Poor coagulopathy profile).
- Recurrent tumor after TACE, RFA, alcohol and microwave ablation.
- Absence of extra hepatic Metastases.

*Once patients fulfilled the inclusion criteria, baseline investigations are done:*

Full medical history and physical examination, laboratory workup including AFP and CT scan or MRI abdomen and pelvis, chest X-ray. Bone scan was done only in case of elevated ALP or symptomatic.

Radiological and Surgical consultation is done for patients to confirm ineligibility of surgery or ablative therapies before deciding radiation treatment.

*Study design:*

Twenty five patients with pathologically or radiologically proven hepatocellular carcinoma presented to kasr el Ainy centre of clinical oncology (NEMROCK) during the period from May 2014 to April 2016 were included in this study. The study evaluated clinical and dosimetric factors related to the occurrence of RILD.

*Follow-up and response assessment:*

Clinical evaluations were planned during treatment at 1,3,6 months after treatment completion. Visits included laboratory assessment (CBC-KFT-LFT). Abdominal CT imaging was done every 3 months during the period of follow-up.

Liver toxicity and GIT toxicity were scored according to NCI common toxicity criteria for adverse events (CTCAE version 3).

*Statistical methods:*

The RILD was computed by the Kaplan-Meier method and compared by the log-rank test and the Cox proportional hazards model. $p$-values less than 0.05 was considered statistically significant. The multivariate Cox model was used to study variation in the RILD occurrence was according to major baseline characteristics (cirrhosis, HCV, child score, BCLC, hepatitis). Statistical analyses were conducted using SPSS software, version 13.0 (SPSS, Inc, Chicago, IL, USA).

## Results

*Patient accrual:*

Twenty five patients with pathologically or radiologically proven hepatocellular carcinoma presented to kasr el Ainy centre of clinical oncology (NEMROCK) during the period from May 2014 to April 2016 were included in this study. They received radiotherapy by the RapidArc technique 50.4Gy/28fr.

*Treatment delivery:*

*1- Total dose of radiotherapy and dose reduction:*

Twenty three patients (92%) completed the full scheduled dose of radiotherapy (50.4Gy), where as two patients only (8%) failed to complete the full dose due to death or intolerable liver toxicity.

Table (1): Total dose of radiotherapy and dose reduction.

| Dose of radiotherapy | Number (dose) | Percent |
|---|---|---|
| | 23 (50.4Gy) | (92) |
| | 1 | (4) |
| | 1 | (4) |

*2- Radiotherapy delivery period:*

Five patients (20%) had interrupted radiation course. The interruption ranged from 5 days to 13 days.

Table (2): Radiotherapy delivery period.

| Treatment delivery | Arm | |
|---|---|---|
| | N (%) | N (Days) |
| Interruption of radiotherapy delivery period | 5 (20) | 1 (13 d)<br>1 (11 d)<br>1 (9 d)<br>1 (5 d)<br>1 (10 d) |

Table (3): Dose constraints of the liver and risk structures.

| Parameter | Mean |
|---|---|
| Normal Liver minus PTV | 15.8Gy (±5.1) |
| V40 liver | 2.62% (±1.52) |
| V30 liver | 16% (±8) |
| V20 liver | 34% (±15) |
| V10 liver | 58% (±19) |
| Stomach | 8.5Gy (±4.8) |
| Lt.kidney | 2.3Gy (±1.5) |
| Rt.kidney | 8Gy (±5.29) |
| Duodenum | 23Gy (±12) |
| Spinal cord | 15.8Gy (±5.1) |

*Radiation toxicity:*

The most common toxicity is RILD representing 28% of the population that received radiotherapy. It occurred within 3 to 6 monthes after radiotherapy.

Toxicity from radiation is mentioned in Table (4) were RILD is the most common significant toxicity observed.

*RILD is classified into two types as follows:*

Classic RILD where there is anicteric hepatomegaly, elevation of ALP level of at least two folds and non malignant ascites (between 2 weeks and 3 months after completion of radiotherapy.

Non classic RILD where there is elevation of transaminases of at least five fold the upper limit of normal or of the pre treatment level (grade 3 or 4 hepatic toxicity of Common Toxicity Criteria Version 2.0 by National Cancer Institute) in the absence of documented progressive disease [8].

Table (4): Radiation toxicity.

| Toxicity | Number (percent) |
|---|---|
| RILD | 7 (28) |
| Gastritis | 3 (12) |
| Deudenitis/ulcer | 3 (12) |
| Easophagitis | 1 (4) |

The factors studied associated with toxicity were mentioned in Table (5) (cirrhosis, HCV, previous intervention, child pugh score, hepatitis, BCLC staging) and Table (6) (PTV volume, V30, V20, V10). We find that the "Mean volume of PTV" is the only factor causing statistically significant difference in the occurrence of RILD. The mean volumes of PTV for the patients who developed RILD and those who didn't was 620.2 and 579.7 respectively with $p$-value=0.028.

Table (5): Correlation between clinical Factors and occurrence of RILD.

| Factor | RILD | No RILD | $p$-value |
|---|---|---|---|
| *Cirrhosis:* | | | |
| No | 0 | 1 | 0.524 |
| Yes | 7 | 17 | |
| *HCV:* | | | |
| No | 2 | 2 | 0.285 |
| Yes | 5 | 16 | |
| *Previous intervention:* | | | |
| No | 5 | 13 | 0.968 |
| Yes | 2 | 5 | |
| *Child score:* | | | |
| A | 4 | 9 | 0.748 |
| B | 3 | 9 | |
| *BCLC:* | | | |
| A | 2 | 7 | 0.88 |
| B | 2 | 4 | |
| C | 3 | 7 | |
| *Hepatitis:* | | | |
| C | 3 | 15 | 0.06 |
| B,C | 2 | 1 | |

Table (6): Correlation between dosimetric data and occurrence of RILD.

| Factor | RILD | No RILD | *p*-value |
|---|---|---|---|
| *Dose to liver- PTV:* | | | |
| Mean | 15.8 Gy | 15.8 Gy | 0.14 |
| SD | ±6.51 Gy | ±4.74 Gy | |
| *Liver-PTV volume:* | | | |
| Mean | 1372.8 | 1349.8 | 0.631 |
| SD | ±217.3 | ±295.2 | |
| *PTV volume:* | | | |
| Mean | 620.2 | 579.7 | 0.028 |
| SD | ±728.1 | ±415 | |
| *V30:* | | | |
| Mean | 13.3% | 16.4% | 0.97 |
| SD | ±9.3% | ±7.4% | |
| *V20:* | | | |
| Mean | 29% | 36% | 0.76 |
| SD | ±16.7% | ±13.8% | |
| *V1 0:* | | | |
| Mean | 50.8% | 61.3% | 0.26 |
| SD | ±22.39% | ±17.91% | |

## Discussion

Because of the advancement in radiation therapy techniques and proper dose constraints, GIT toxicity (stomach, duodenum) and spinal cord toxicity has been reduced, however RILD is still the most prominent complication in patients with hepatic radiation.

*RILD is classified into two types as follows:*

Classic RILD and non classic RILD as mentioned.

Majority of our patients are HCV carriers and cirrhotic, thus hepatocytes are more susceptible to radiation injury. The most common important toxicity is RILD occurred in 7 patients (28%).

After studying several factors associated with RLID, we found that as the mean PTV volume increases, the higher risk of occurrence of RILD, where the mean of PTV volumes for the 7 patients who developed RILD was 620cm$^3$ vs 579.7cm$^3$ for the 18 patients who were RILD free, with *p*-value=0.028.

Min et al reported that hepatic toxicity increases as the irradiated dose to normal liver increase. In the study RILD occurred in 12 patients (44%) of the population and mean dose to normal liver 15.8 Gy **[9]**.

Cheng et al., also reported that mean liver dose of patients with RILD was significantly higher than those without (25Gy vs 19.65Gy, *p*-value 0.02) **[10]**.

Pan CC et al., recommended that the mean normal liver dose should be less than 28Gy in 2Gy fractions for primary liver cancer **[11]**.

Similar dose constraint to normal liver used in our study which was even lower than the previously mentioned. We used 24Gy as maximum tolerance dose to the liver based on the Quantec model.

Compared to the above studies, its clear that our mean dose to normal liver minus PTV was 15.8Gy±5.1 was lower than the previously mentioned in the above studies and so it has no significant difference in the occurrence of RILD with *p*-value=0. 14.

Combined modality treatment is another factor to be correlated with RILD, where we can find in many studies that radiotherapy combined with TACE or non-selective hepatic arterial chemotherapy give a higher rate of hepatic toxicity than radiotherapy alone **[12-14]**.

No statistical significant difference was observed in the occurrence of RILD between those who received combined modality and those who didn't, may be due to small sample size and even less number of patients who underwent previous treatments or it is related to multiplicity of local treatments received by the patients in these studies which higher the toxicity compared to our patients who received only single modality prior to radiation.

The value of V30 was found to play an important role in the development of RILD in patients treated with conventional radiotherapy **[15]**.

Kim et al., also reported that the low dose coverage V5 and V10 were associated with toxicity but the potential risk of RILD by low dose radiation is still unclear.

Also the value V20 was significant parameter for development of RILD after conventional radiotherapy as reported by Liang et al., **[16]**.

In a recent study of Dong Cheng et al., where it compared between the 3 techniques CRT, IMRT, Rapid Arc in treatment of advanced HCC, found that RapidArc was superior at the risk of RILD in consideration of lower V20 and V30 **[17]**.

On the other hand, similar comparative study Kuo et al., reported that rapid arc has higher V1 0 and D mean compared to IMRT which should be taken with caution when treating HCC patients since its associated with RILD as mentioned before.

Regarding our study, no significant difference was shown in the occurance of RILD with V 10, 20 and 30, which is probably due to the lower mean dose to normal liver (15.8Gy) and as a result the mean of V 10,20,30 will also be lower compared to other studies.

In addition to dose-related factors affecting RILD, Cheng et al., reported that patients with Child Pugh-B or hepatitis B virus (HBV) are also at a significant risk of developing RILD. Patients with CP-B had worse hepatic insufficiency compared with those with CP-A **[18,19]**.

CP-B has a higher hepatic toxicity compared with CP-A. This was not obvious in our study due to our smaller sample size which failed to show statistical significant difference between both groups.

HBV rather than hepatitis HCV infection was also associated with higher RILD. Because HBV carriers have poor tolerance to partial liver irradiation **[18-20]**.

The group of patients who received radiation in our study, none of them had isolated HBV infection, the majority were HCV carriers and 3 patients had Co-infection B and C and though we couldn't assess HBV as a separate entity and there was no statistical significance also.

Limitations of our study include, small sample size, relatively coarse 5mm slice thickness and lack of a specific strategy to compensate for liver motion due to respiration. Respiratory gating techniques are not available in the department. Also abdominal compression and breath control are not easily feasible in our patients.

The potential displacement of liver could be as large as 2-2.5cm **[20]**, its suggested to incorporate motion compensation into traditional definition of margins.

*Follow-up of patients:*

Most of the patients completed the course of radiotherapy except 2 patients had intolerable hepatic toxicity and one died of liver cell failure.

The rest of the patients who developed RILD recovered with liver support, hydration and steroids.

*Conclusion:*

The most common toxicity with radiation is RILD (28%) and the most important significant factor associated With RILD is the PTV volume.

Gastritis, duodenitis and esophagitis were also seen but with less impact on toxicity.

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# العلاج الأشعاعى (RILD) فى مرضى سرطان الكبد

سرطان الكبد قد أصبح خامس الأورام السرطانية شيوعاً وثالثها كسبب للوفاة من السرطان على مستوى العالم مع إرتفاع معدل وقوعه فى مصر. وحالياً يعد أكثر الأورام السرطانية شيوعاً فى مصر بين الذكور.

فى الفترة الأخيرة برز دور العلاج الأشعاعى مع إزدياد إستعماله لعلاج سرطان الخلايا الكبدية المتقدم والغير قابل للعلاج الجراحى حيث تقل جداً الخيارات العلاجية.

تهدف هذه الدراسة إلى مقارنة العلاج الأشعاعى بالأقواس الحجمى المعدل الشدة (VMAT) بالعلاج التدعيمى فى علاج مرضى سرطان الخلايا الكبدية المتقدم الغير قابل للجراحة مع مقارنة معدل البقاء الناتج. كما تهدف الدراسة إلى تقييم فاعلية وأمان إستخدام ال VMAT فى هذه الحالات.

جرى هذا البحث بمركز قصر العينى لعلاج والطب النووى بجامعة القاهرة، على عدد خمسين حالة من حالات سرطان الخلايا الكبدية المتقدم فى الفترة من مايو ٢٠١٤ حتى أبريل ٢٠١٦. أظهرت تحليل البيانات تفوق العلاج الأشعاعى (VMAT) على العلاج التدعيمى من ناحية فترة البقاء بدون تقدم كان متوسطها ٦.٩ شهراً فى حالة العلاج الأشعاعى مقارنة ب ٥.٩ شهراً فى حالة العلاج التدعيمى، وكان الفارق ذو دلالة إحصائية هامة ( قيمة $p$=٠.٠٠١) وبلغت نسبة الإستجابة للعلاج ٤٤٪.

وجد أن أكثر الأعراض الجانبية شيوعاً لدى المرضى الذين تلقوا العلاج الأشعاعى هو مرض الكبد الناتج عن الأشعاع (RILD) حيث أصاب ٢٨٪ منهم. ويعتبر حجم الورم من أكثر العوامل المؤثرة فى حدوثه.