Radiological Spectrum of Hepatocellular Carcinoma in Pakistan: Are we diagnosing too late

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Abstract

Background: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third cause of cancer-related deaths. Chronic liver disease due to chronic viral hepatitis is the major cause and burden is increasing especially in the developing countries including Pakistan. Early diagnosis of HCC is the key to the cure of the disease.

Objective: The objective of this study was to look for the characteristics of HCC on a multiphasic Computerized Tomography (CT) scan at the time of diagnosis. These CT scan reports were evaluated for a potential candidacy of curative therapy.

Methods: All multiphasic CT scans done at our institute from June 2017 to June 2019 with a diagnosis of new HCC were evaluated. Demographic data like age, gender, presence of liver cirrhosis, cause of liver cirrhosis, size & site of the tumor, portal vein thrombosis, and presence of metastasis were noted. Data were analyzed for the potential candidacy of curative treatments like hepatic resection, radiofrequency ablation, and liver transplant.

Results: 106 cases of HCC were found. 73 (69%) were males, median age of our patients was 49.6 $\pm$ 12.3yrs. 97 patients (92%) had radiological evidence of liver cirrhosis and HCV infection 76(71.7%) was the major cause of liver disease followed by NBNC cirrhosis 24 (22.6%) and HBV 6(5.6%) infection.48 cases (45.3%) had involvement of both lobes of the liver, 46 (43.4%) had involvement of right lobe while 8(7.5%) had involvement of only the left lobe of the liver. 44 (41.5%) patients had evidence of portal vein thrombosis

at the time of diagnosis proving vascular invasion of the tumor. 6 (5.6%) patients had evidence of distant metastasis while 23(21.7%) had evidence of lymphadenopathy. According to the latest guidelines for the treatment of HCC, only 39 (36.8%) were potential candidates for curative therapy i.e. tumor resection, radio frequency ablation (RFA) or liver transplant on the bases of radiological findings.

Conclusion: HCC is a serious and common complication of liver cirrhosis. We need to strengthen our surveillance strategies to diagnose earlier so a cure could be offered to these patients.

Keywords: Radiological, Spectrum, Hepatocellular Carcinoma. Pakistan, cirrhosis.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third cause of cancer-related deaths as estimated by the World Health Organization [1]. The incidence of HCC is growing worldwide, and liver cirrhosis due to viral hepatitis represents a major risk factor for the development of HCC [2]. In the United States of America, there is progressive increase in HCC due to obesity-related fatty liver disease over the past two decades [3]. Almost 85% of HCC cases are estimated to occur in low resource or middle- resource countries, particularly in Eastern Asia and sub- Saharan Africa [4]. Exact prevalence of HCC in Pakistan is not known and data is mostly confined to single-center registries. Pakistan contains one of the biggest burdens of chronic hepatitis C (CHC) patients and it is conceivable that the prevalence of HCC may be high and it is going to increase in the future [5].

Early diagnosis of HCC is the key to cure, as many therapeutic options are available if we diagnose at an early stage. However, incidence and cancer-specific mortality still continue to increase and the majority of HCC patients still present at an advanced stage in many parts of the world [6]. All major societies recommend surveillance strategies for early detection and better management of HCC [7,8]. Traditionally, HCC was diagnosed on the bases of tumor markers, radiological features, and histopathology. Following advances in understanding HCC- specific radiological features during phasic vascular perfusion of contrast during cross-sectional imaging with computerized tomography (CT) and magnetic resonance imaging (MRI), the diagnosis of HCC in patients with cirrhosis who are under surveillance can now be made reliably without a biopsy. The American Association for the Study of Liver Diseases (AASLD) and European Association for Study of Liver (EASL) guidelines state that the diagnosis of HCC can be made radiologically if a new mass measuring ≥1 cm is found that demonstrates arterial hyperenhancement and venous washout in a cirrhotic liver using multiphasic contrast CT [7,8]. It is essential to use the imaging modalities deliberately and liberally to confidently detect early lesions; thereby allowing effective and curative treatment options for HCC.

Treatment of HCC involves a complex decision-making process involving hepatic functional status, co-morbids, and characteristics of hepatocellular carcinoma on a multiphasic CT scan. Curative options for HCC are hepatic resection, liver transplantation and focal ablation by either microwave or radiation. The radiological characteristics of hepatocellular carcinomas like the size of the tumor, site of the tumor, no of focal lesions, vascular invasion and metastasis are very important determinants of the treatment plan. Liver transplantation is an excellent treatment for early-stage HCC. The Milan criteria (one lesion <5 cm or two

or three lesions each <3 cm) were established to define the optimum tumor burden for which liver transplants can achieve excellent long- term outcomes [9]. The determination of hepatic focal lesion for respectability is based on anatomical considerations, number and location of tumors, the anticipated volume of resection and hepatic functional reserve. According to the guidance statements by AASLD, thermal ablative techniques have the best efficacy in tumors with a maximum diameter of less than 3 cm [8].

Pakistan harbors one of the highest burdens of hepatocellular carcinoma in the world. Due to limited healthcare facilities in Pakistan, we do not have a well-established surveillance system for the early diagnosis of HCC. This study was conducted to (1) look for the radiological spectrum of hepatocellular carcinoma on multiphasic CT scan at the time of diagnosis and (2) to evaluate how many of our HCC patients could be offered curative treatment options on the basis of CT scan at the time of diagnosis. Another thought was to give a stringent message for strengthening surveillance strategies in high-risk patients.

Material & Methods

- This is an observational cross-sectional study.
- Multiphasic CT scans done at the Department of Radiology, Madina Teaching Hospital Faisalabad from June 2017 to June 2019 with a diagnosis of new HCC were evaluated.
- Demographic data like age, gender, presence of liver cirrhosis, cause of liver cirrhosis, size & site of the tumor, portal vein thrombosis, and presence of metastasis were noted.
- Liver cirrhosis was diagnosed on the basis of hepatic parenchymal changes, nodularity and irregularity of the liver along with the presence of ascites and size of the spleen.

- Only newly diagnosed hepatocellular carcinoma cases were evaluated.
- Patients with a previous history of HCC or with history of any treatment for HCC were excluded from the study
- Data was analyzed for the potential candidacy of curative treatment according to the criteria of Barcelona Criteria for Liver Cancer (BCLC).
- According to BCLC criteria, patients with radiological Stage 0 and stage A (Single nodule <5cm or 2-3 nodules, largest <3cm) at the time of diagnosis were considered illegible for a curative therapy i.e either liver transplantation, hepatic resection and radiofrequency ablation or microwave ablation.
- Data was entered and analyzed using SPSS version 22.
- Mean $\pm$ SD, ranges were calculated for continuous variables and proportions for categorical variables.

This study was conducted in accordance with the Helsinki Declaration and was approved by the ethical review committee of the University of Faisalabad.

Results

During the study period, a total of 106 cases of newly diagnosed HCC were found. The majority of the patients were males i.e 73 (69%) while 33 (31%) were females. The median age of our patients was 49.6 $\pm$ 12.3yrs. 97 patients (92%) had radiological evidence of liver cirrhosis. HCV infection, 76(71.7%) was the major cause of liver disease in our patients followed by NBNC cirrhosis in 24 (22.6%) and HBV 6(5.6%) infection as shown in Fig 1.
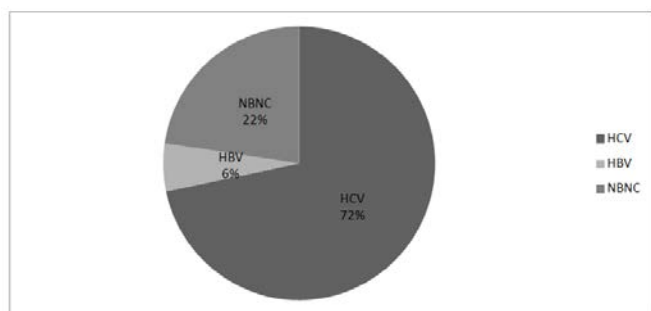
Fig.1: Etiology of liver disease in patients with hepatocellular carcinoma. (n=106)

48 cases (45.3%) had involvement of both lobes of the liver, 46 (43.4%) had involvement of right lobe while 8(7.5%) had involvement of only the left lobe of the liver. 44 (41.5%) patients had evidence of portal vein thrombosis at the time of diagnosis proving vascular invasion of the tumor. 6 (5.6%) patients had evidence of distant metastasis while 23(21.7%) had evidence of lymphadenopathy. The radiological spectrum of hepatocellular carcinoma is shown in table 1.

Table 1; Radiological characteristics of Hepatocellular carcinoma at the time of diagnosis.

(N= 106)

Characteristics	Number	Percentage
Multi Lobular	48	45%
Single Lobe	58	55%
Single Nodule	21	19.8%
Multifocal	85	80.2%
Portal Vein thrombosis	44	41.5%
Tumor size less than 5cm	36	34%
Tumor size more than 5cm	70	66%
Metastasis	6	5.7%
Lymph Nodes involvement	23	21.7%

According to the latest Barcelona Criteria of Liver cancer guidelines for the treatment of HCC, only 39 (36.8%) were potential candidates for curative therapy i.e. tumor resection, RFA or liver transplant on the bases of radiological findings. In the remaining patients, the tumor has already so advanced at the time of diagnosis that curative treatment could not be offered and they were candidates for palliative or supportive care only. (Fig.2)
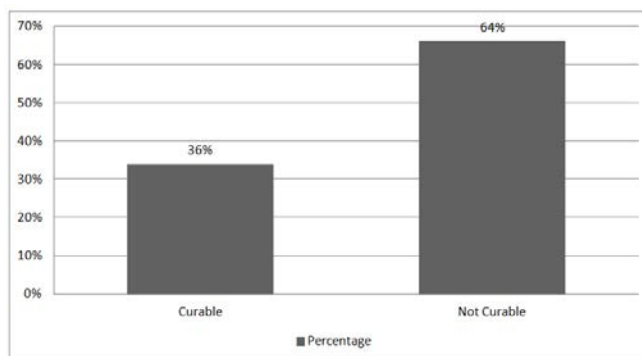

Fig. 2: BCLC Stage 0 & 1. Candidates for curable therapy at the time of diagnosis (n=106)

Discussion

Hepatocellular carcinoma is the most devastating complication of liver cirrhosis. In spite of major advancements in the diagnostic tools and management of HCC, incidence and cancer-specific mortality still continue to increase in many countries and the majority of HCC patients still present at an advanced stage [6]. There has been significant improvement in the radiological diagnosis of HCC and modern radiology plays an important role in the evaluation and treatment. In 2011, the Liver Imaging Reporting and Data System (LI-RADS) was introduced to standardize the reporting and data collection of CT and MRI for HCC. (10) LI-RADS classifies new hepatic lesions into five classes based on their size, extent of interval growth and patterns of enhancement [11].

Surveillance for HCC is an important strategy to decrease morbidity and mortality in high-risk patients. Surveillance for HCC has been recommended by most of the hepatic societies [7,8]. A meta-analysis of 47 studies including 15,158 patients found that HCC surveillance is associated with improved overall

survival through detection of HCC at a very early or early stage when patients are eligible to receive potentially curative treatments [12]. In our study, the mean age of the patients was 49.6 years. AS Butt and colleagues in their review of 29 studies of HCC from Pakistan reported that most patients presented during the fifth decade of life [13]. HCC tends to occur later in life in Europe, Japan and North American countries where the median age of onset is above 60 years. Whereas in Asia and Africa HCC is diagnosed earlier with an age range of 30-60 years [14].

Majority of the patients in our study were males (69%). This is a consistent finding in almost all studies done from our country [5,13] as well as international data persistently reported that males are affected more than females, the sex ratio usually ranging between 2:1 and 4:1 [1]. This gender difference in the development of HCC is due to the effect of sex hormones testosterone and estradiol on hepatocarcinogenesis [15]. Chronic hepatitis C (72%) was the major cause of HCC in our study as reported previously from Pakistan [16]. HCV is the leading virus-related cause of HCC in North America, Europe, Japan, parts of central Asia including Mongolia, and northern Africa and the Middle East, particularly Egypt [17] 22% of our patients had non-viral etiology which is slightly different from previous studies from Pakistan [5,13] but internationally fatty liver disease is now the main common liver disease and a major risk factor for HCC. [18,19].

Management of HCC involves a complex decision-making process, taking into account not only the tumor extent and patient comorbidities but also the severity of liver dysfunction. Early detection is the key to success as most of the curative treatment options could be offered to early-stage disease. In our study, only 34% of patients were diagnosed in the early stage where a curative option (Resection, ablation or transplantation) could be offered. The same results of diagnosis of HCC at an advanced stage (62.8%) were reported by a study from Aga Khan Hospital Karachi by Butt AS and colleagues [5]. Stage of the disease at the time of diagnosis is the main determinant of the survival of the patients which varies substantially across the world. [14,17] On the other hand, Japan and Taiwan have the best outcomes of the patients with HCC. >70% of HCCs diagnosed at major medical centers in these countries are detected at very early or early stages and are eligible for curative therapies [20]. This is likely because both countries have comprehensive programs for identifying all adults at risk of HCC and enrolling them in regular, intensive liver cancer surveillance programs. >60% of patients present in an intermediate or advanced stage in China North America and Europe so the outcomes are not very good in these parts of the world [20]

Our study has some limitations as it is a single-center study and we have not incorporated other data in the decision making of treatment for cure.

Conclusion

HCC is a serious and common complication of liver cirrhosis. Many patients are being diagnosed in advanced stages so curative therapy is not possible. We need to strengthen our surveillance strategies to diagnose earlier so a cure could be offered to these patients.

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