SCIENTIFIC ARTICLE

Hepatocellular carcinoma in Sri Lanka - where do we stand?

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ABSTRACT

Hepato-cellular carcinoma (HCC) is the sixth commonest cancer and third in cancer-related mortality worldwide. There are no published reports on the pattern of HCC in Sri Lanka. North Colombo Liver Unit maintains a prospective database of 105 HCC patients from September 2011. HCC was diagnosed based on characteristic radiological appearance. Best form of treatment was decided by a multidisciplinary team (MDT). Median age at presentation 63 (12 - 79) years. 87% (n=93) males. 45% (n= 47) had alcohol consumption above safe limits .41% (n=53) had diabetes. Cirrhosis was present in 79% (n=83) .median Model for End Stage Liver Disease (MELD) score 12 (4-22); Childs- Pugh class A 45% (n=37), Childs-Pugh class B or C 55% (n=46)]. A biopsy was necessary in 7 (6.6%) while others were diagnosed on radiology .62.5% had AFP level above the reference range (> 10 ng/ml). 51(49%) had a single modality, 17 (16%) had combined treatment and the rest had no treatment. The overall mean survival was 15 months

Majority of HCCs in Sri Lanka were among males and is likely to be secondary to NASH related cirrhosis. Majority of the tumours were diagnosed at late stage.

Key words: Hepato-cellular carcinoma; HCC; Meld score

Introduction

Hepato-cellular carcinoma (HCC) is the sixth commonest cancer worldwide. It's poor prognosis has ranked it third in cancer-related mortality [1]. The majority of HCCs arise in cirrhotic livers. Causes that lead to cirrhosis closely associate with HCC. Worldwide, hepatitis B virus (HBV) is responsible for 50%-80% of HCC cases and 10%-25% are thought to arise in hepatitis C virus (HCV) infected livers [2]. Nonalcoholic fatty liver disease (NAFLD) has become an epidemic in Asia. Patients with active form of NAFLD, namely steatohepatitis (NASH), have progressive hepatocellular injury and fibrosis. They eventually develop cirrhosis. NASH-related cirrhosis has similar mortality to those with other causes of cirrhosis and the risk of developing hepatocellular carcinoma is up to 2-3% per year [3]. HBV is not endemic in Sri Lanka with a incidence of less than 1%, while NAFLD is becoming a serious health concern in the country [4]. There are no published reports on the pattern of HCC in Sri Lanka. This study looks at hundred consecutive patients with HCC in a tertiary referral centre.

Materials and Methods

North Colombo Liver Unit maintains a prospective database of all patients referred from September 2011. HCC was diagnosed based on accepted characteristic radiological appearance on multidetector contrast CT or dynamic MRI. In cirrhotic livers, single mode of imaging was considered adequate. A second mode of imaging was done in doubtful lesions and in patients with normal background liver. Biopsy was performed only in lesions larger than 1 cm having atypical radiological appearance on two imaging modalities.

Decision on the best form of treatment was taken by a multidisciplinary team (MDT). The MDT consisted hepatologists, hepatobiliary and transplant surgeons, radiologists, oncologists and pathologists. Treatment was based on the liver function, residual liver volume, nature of the tumour and patients functional status. Liver function was assessed based on the Child score, degree of portal hypertension, and the computed tomogram (CT) appearance of the liver. Surgery or liver transplantation was considered for patients with potentially curable disease. Percutaneous ethanol injection (PEI) or radio frequency ablation (RFA) for lesion < 2 cm and RFA for lesions < 5 cm was done for unresectable lesions, visible on ultrasound scan, with a curative intent. In others disease was treated aggressively with the intention of delaying the disease progression. Trans-arterial chemo embolization (TACE) was used liberally as a single mode or combined treatment. For lesions larger than 10cm in diameter or lesions with major vascular involvement, trans-arterial chemotherapy (TAC) was performed without embolising the artery. Sorafinib was prescribed for selected patients when none of the other

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treatment options were feasible. Concurrent to the definitive treatment, management of underlying cirrhosis was supervised by a team of hepatologists.

Results

There were 105 entries in the registry by February 2013. The median age at the presentation was 63 (12 - 79) years. Patients were predominantly (87% [n=93]) males. Half of the HCCs were detected when they were investigated for trivial symptoms like abdominal discomfort, pain and low grade fever. Regular alcohol consumption above safe limits was reported in 45% (n= 47) of the patients. 34% (n= 36) of the cases had no history of alcohol consumption. Fifty one percent (n=53) of the patients had diabetes. Screening for hepatitis B by Hepatitis B surface antigen was carried out in 45 patients and all of them were negative for the surface antigen.

Background liver cirrhosis was evident in 79% (n=83) of the patients. The median uncorrected model for end stage liver disease (MELD) score was 12 (4-22). 45% (n=37) of the cirrhotics were of Childs- Pugh class A. 55% (n=46) were either Childs-Pugh class B or C. Esophageal varices were not detected in 85% (n= 71). 45% (n=37) of the patients had some degree of ascites.

A liver biopsy for diagnosis was necessary in 7 (6.6%) cases. All the others were diagnosed based on radiological appearance. The median tumour diameter at the detection was 6 cm (1.8-25 cm). 46% (n=48) of the patients had single nodular tumours while 21% (n=22) had diffusely infiltrating tumours. Extra hepatic metastasis was detected in 3 patients at the time of the diagnosis of HCC. Portal vein invasion was seen in 22 (20 %) patients. Hepatic vein and inferior vena cava was involved in two cases. Median alpha-feto protein level was 57.25 mg/ml (1.16- 94120 ng/ml; n=72). There were 62.5% of the patients having AFP level above the reference range (> 10 ng/ml). 33% had AFP level more than 400 ng/ml.

Fifty one patients had only single modality of treatment. 17 patients had combined treatment and the rest had no treatment. Surgery was performed in 18 (17%), liver transplant in 2 (1.9%), radiofrequency ablation or alcohol ablation in 8 (7.6%), TACE/TAC in 44 (42%) and Sorafinib was prescribed for four patients. The commonest combination was trans- arterial treatment and surgery. The maximum follow-up period was 25 months. The overall mean survival of the group was 15 months. No treatment arm had an overall survival of 4 months. TACE and ablation group had median survival of 16 and 15 months respectively. Surgery group had a mean survival of 20 months (figure 1).

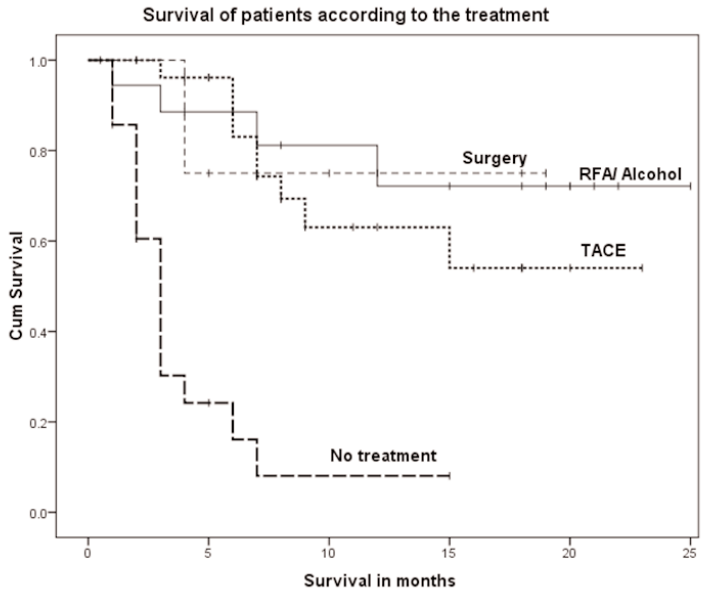

Figure 1. Kaplan-Meier survival curve of the four groups of patients categorized according to the predominant mode of treatment. Long rank test comparing the survival of treatment and no treatment groups p<0.005.

RFA- Radiofrequency ablation, TACE- Trans arterial chemo embolization.

Table 1. Baseline characteristics of patients at presentation

Background liver status	
Bilirubin (mg/dl)	1.15 (0.2-13.7)
Albumin (mg/dl)	3.3(2.23-4.7)
MELD score	12 (4-22)
Childs score	7 (5-14)
Child class	Class A- 37 (44.6%) Class B- 29 (34.9%) Class C- 17 (20.4%)
Non tumour liver	
Normal	20 (19%)
Hepatitis/fibrotic	2 (2%)
Cirrhosis	83 (79%)
Tumour type	Single nodular – 48 (46.2%) Multiple one lobe – 14 (12.9%) Multiple both lobes – 21 (20%) Diffuse -22 (21.5%)
Local invasion	None – 66(62.8%) IVC – 2 (2%) Portal vein – 37 (35.2%)
Extra hepatic metastasis	Lung -3 (2.8%)
Maximum tumour diameter (cm)	6 (1.8-25)
AFP (ng/ml)	57.25 (1.16-94120)

MELD -model for end stage liver disease, AFP - alpha-feto protein

Table 2. Treatment summary

Type of treatment	Total Number of patients	Patients alive	Patients dead	Survival (%)
Surgery alone (resection)	8	7	1	87.5
Surgery and TACE/TAC	7	5	2	71.4
Surgery and RFA	2	2	0	100
Surgery and Alcohol	1	0	1	0
Liver Transplant	2	2	0	100
TACE/ TAC alone	32	20	12	62.5
TACE and RFA	1	1	0	100
TACE and Alcohol	3	3	0	100
TACE and Sorafinib	1	0	1	0
RFA alone	3	3	0	100
Alcohol alone	3	2	1	66.6
Sorafinib alone	3	1	2	33.3
RFA and Alcohol	2	2	0	100
No treatment	37	8	29	21.6

TACE - Trans arterial chemo embolization, TAC - Trans arterial chemotherapy, RFA - radiofrequency ablation.

Discussion

NAFLD alone or in combination with alcohol was the predominant cause of HCC in our cohort. Infective hepatitis was not detected in our group. Disease was mainly among males. Majority of the tumours were diagnosed at late stage when the size was more than 5cm. Large proportion of our patients had vascular invasion and were also having poor prognostic diffuse type cancers at the presentation.

Male to female ratio, according to American cancer society data is 1 to 2.6 [5]. Data from European centers show a similar pattern [6]. In our population males are affected four times more than females. This seems to be the pattern in south Asian and east Asian populations where a higher male preponderance is seen compared to the west [7-9]. It is interesting to note this regional similarity despite the difference in the etiology of HCC in our patients.

In half our patients exact cause of cirrhosis was not detected. These patients were attributed to NASH related cirrhosis. Others gave a history of alcohol consumption in

significant amounts. Dassanayake et al detected that up to 40% of the Sri Lankan urban population had ultra sound detected fatty liver at the median age of 52 years [4].In our cohort of patients who had history of alcohol consumption, it may not be the sole cause for cirrhosis. The median age being 61years, a significant proportion of these could have had underlying NASH on top of alcohol addiction. Further consideration needs whether alcohol acts as a contributor for developing HCC in NASH patients.

Our data shows that 33% had a significant elevation of AFP over 400 u/l and 62% had non-diagnostic elevation. These figures are similar to the reports from east and west [6,9]. Though the AFP level was diagnostic in only one third, in others level was helpful in the follow-up once the HCC was diagnosed and treated.

In conclusion, majority of HCCs in Sri Lanka were among males and is likely to be secondary to NASH related cirrhosis. Majority of the tumours were diagnosed at late stage.

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