INTRODUCTION
Hepatitis C (HCV) is a common disease worldwide and is much more prevalent in Pakistan.\textsuperscript{1} It has the tendency to develop progressive fibrosis and cirrhosis and can result in hepatocellular carcinoma (HCC) over time.\textsuperscript{2} Since the introduction of treatment with interferon (IFN) and later with ribavirin (RIB), the response rate of patients with hepatitis C has improved significantly. In Pakistan, genotypes-2 and 3 are the commonest and 80\% patients achieve sustained virological response (SVR).\textsuperscript{3} Many previous studies had reported similar results and hypothesis has been that treatment of hepatitis C and achieving a sustained virological response (SVR)\textsuperscript{3} is likely to prevent the complications of HCV infection including hepatocellular carcinoma.\textsuperscript{4,5} More studies were reported lately suggesting that HCC risk is lower in HCV patients who achieved SVR.\textsuperscript{6-10} In a meta-analysis of 1505 HCV patients, treated with interferon and ribavirin and who achieved SVR, showed that IFN therapy significantly decreased the overall HCC incidence in HCV-related cirrhotic patients.\textsuperscript{7} The authors earlier documented the treatment of patients with chronic liver disease (CLD) with 47\% SVR, however, long-term follow-up of these patients is needed to assess the development of complications of CLD in these patients, including HCC.\textsuperscript{11} The aim of this study was to determine the incidence of HCC in HCV-related cirrhosis treated with IFN and RIB who achieved SVR.

METHODOLOGY
The study was a retrospective review of patients treated from January 2007 to January 2012 at Shifa International Hospital, Islamabad, Pakistan. Informed consent was taken from all patients. They were treated with standard doses of IFN and RIB, and in some cases, along with amantidine 100 mg PO BID orally for 6 – 12 months. After the patients had achieved SVR, they were followed every 1 – 2 months for management of cirrhosis. Surveillance of HCC with alpha-feto-protein and ultrasonography was carried out every 6 months. If there was any suspicious lesion, dynamic CT scan was performed. All patients were followed for a mean of 48 ± 17 months with the idea of detecting HCC development in these patients.
All data was analyzed using Statistical Package for Social Sciences (SPSS) version 17. General descriptive analyses were performed to compare participants with and without HCC. Variables were compared using Pearson come chi-square or Fisher's exact tests or t-tests as applicable. P-value of less than 0.05 was considered significant.

**RESULTS**

A total of 58 patients who had SVR were followed. There were 41 male and 17 female patients. Mean age was 52 ± 13 years.

Out of a total of 58 patients, 3 developed HCC. This was confirmed by elevated alpha-feto-protein and dynamic liver CT scan.

Two patients had multifocal HCC and one had single lesion (Table I). Two patients with multifocal disease died as a result of hepatic encephalopathy. One with single lesion refused any therapeutic intervention and is still living. Baseline characteristics of patients with and without HCC did not differ (Table II).

**DISCUSSION**

Hepatitis C is a viral infection that progresses to fibrosis and cirrhosis and ultimately has the tendency to develop HCC. The disease is worldwide and has significantly more prevalent in Pakistan. In this study, 3 patients developed HCC; 2 of the lesions were multifocal in nature. In these patients, other complications of CLD also developed which included recurrent hepatic encephalopathy and recurrent GI bleeding.

Hepatocellular failure is a natural consequence of cirrhosis with hepatic encephalopathy as its end result. This happens due to disturbance in ammonia metabolism with resultant effects on brain.

Two of these patients developed this during the course of illness. First patient developed this before the discovery of his HCC. Both patients survived the episode but when HCC was discovered, the course was more rapidly downhill, as has been well documented. Portal hypertension and variceal bleeding are common terminal events in cirrhosis. The first and second patients suffered recurrent esophageal variceal haemorrhage. The third patient did not develop complications of hepatocellular failure and portal hypertension so far.

Hepatocellular carcinoma is most dreaded complication of hepatitis C. Hepatitis C virus affects the liver in multiple ways; however, mechanism of carcinogenesis remains a subject of discussion. In spite of apparently decreased rate of development of HCC after IFN treatment, several studies have reported occurrence of this cancer in HCV related cirrhosis. Five prospective studies from Europe and the US have shown that during the first 10 – 15 years after initial infection, liver cancer is a rare occurrence. In patients with hepatitis C, there is an increased risk of HCC coinciding with the establishment of cirrhosis with yearly incidence between 3 – 8%. In Japan, the mean interval between infection and development of HCC is 30 years and a long-time lag of mean of 28 years between transfusion-associated hepatitis and development of HCC was reported. These patients’ lag time from infection to HCC was unknown but was shorter on follow-up after treatment than reported in the above studies.

The role of confounding factors in carcinogenesis of these patients has to be considered. Diabetes mellitus has been reported to have a selective impact on HCC development among HCV patients after IFN-based therapy and may increase the HCC risk in them. The first patient had diabetes but was not of more than 5 years duration. Male gender and old age were independent significant risk factors contributing to HCC development. All of these patients were old males. Cirrhosis of the liver has been regarded as a pre-malignant condition independent of its etiology, as more than 80% of HCC developed in a cirrhotic liver. Alcohol, obesity, smoking and non-alcoholic fatty liver disease have also been known factors that may contribute to hepatic carcinogenesis. However, none of these patients had any of these factors.

**Table I:** Profile of CHC patients with SVR developing HCC.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Gender</th>
<th>CPT</th>
<th>MELD score</th>
<th>Time of diagnosis of hepatitis C</th>
<th>Time of SVR</th>
<th>Time of diagnosis of HCC</th>
<th>Number of years from SVR to HCC</th>
<th>Other complications</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>C</td>
<td>22</td>
<td>2004</td>
<td>2005</td>
<td>2012</td>
<td>7</td>
<td>GI bleeding</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>M</td>
<td>B</td>
<td>14</td>
<td>2001</td>
<td>2003</td>
<td>2011</td>
<td>7</td>
<td>Hepatic encephalopathy</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>M</td>
<td>A</td>
<td>12</td>
<td>2003</td>
<td>2004</td>
<td>2012</td>
<td>8</td>
<td>None</td>
<td>Alive</td>
</tr>
</tbody>
</table>

*CHC = Chronic hepatitis C; SVR = Sustained virological response; HCC = Hepatocellulalr carcinoma; CPT = Child pugh turcot.

**Table II:** Baseline characteristics of HCC and non-HCC patients.

<table>
<thead>
<tr>
<th></th>
<th>HCC (n = 3)</th>
<th>Non HCC (n = 55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.6± 8</td>
<td>52±13</td>
<td>0.32</td>
</tr>
<tr>
<td>Gender (M / F)</td>
<td>3 / 0</td>
<td>38 / 17</td>
<td>0.257</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23 ± 0.16</td>
<td>24 ± 0.55</td>
<td>0.002</td>
</tr>
<tr>
<td>ALT level</td>
<td>82 ± 9</td>
<td>91 ± 15</td>
<td>0.310</td>
</tr>
<tr>
<td>Child class (A/B/C)</td>
<td>1 / 1 / 1</td>
<td>27 / 19 / 9</td>
<td>0.732</td>
</tr>
<tr>
<td>MELD score</td>
<td>11 ± 5</td>
<td>9 ± 7</td>
<td>0.628</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.97 ± 0.33</td>
<td>0.84 ± 0.44</td>
<td>0.721</td>
</tr>
</tbody>
</table>

P-value less than 0.05 considered significant.

All data was analyzed using Statistical Package for Social Sciences (SPSS) version 17. General descriptive analyses were performed to compare participants with and without HCC. Variables were compared using Pearson come chi-square or Fisher's exact tests or t-tests as applicable. P-value of less than 0.05 was considered significant.
The molecular pathogenesis by which HCV contributes to cell transformation remains unclear. It is probable that malignant transformation is related to continuous or recurring cycles of hepatocyte necrosis and regeneration and resulting accelerated cell turnover rate may act as tumour promoter by increasing the probability of spontaneous mutations or damage to DNA by exogenous factors. Malignant transformation may result from the generation of mutagenic reactive oxygen species such as nitric oxide, superoxide anion, hydroxyl radical and hydrogen peroxide resulting in the inflammatory process. Another mechanism of HCV-induced hepatocarcinogenesis may be that HCV has a direct oncogenic action. Viral replication might cause inappropriate expression of two growth factors that may be implicated in hepatic carcinogenesis: transforming growth factor and insulin-like growth factor. The HCV core protein could function as a gene-regulator and after mutation, can inhibit tumour suppressor genes such as p53, as has been demonstrated in hepatic oncogenesis.

One reason for development of HCC in these patients who SVR after IFN, is persistence of HCV in hepatocytes and peripheral blood mono-nuclear cells in the absence of detectable viremia. This “occult hepatitis C infection” causes ongoing hepatic necroinflammatory activity, and hence fibrosis, then this entity may conceivably play a pathogenic role in the antiviral “sustained responding” HCV patient who subsequently develops HCC.

The mechanisms by which an interferon treatment might reduce the risk of HCC in cirrhosis caused by HCV is unclear. Maintenance of serum transaminases at low levels may protect against the development of HCC as hepatocyte necrosis, cell damage and increase in hepatocyte replication result in increased DNA damage, influencing hepatocarcinogenesis. However, there appears to be no rationale for utilizing IFN maintenance therapy in patients with cirrhosis as this approach does not reduce the risk of HCC.

Patient with HCV-related cirrhosis have need for treatment to eradicate the virus so that the disease process can be arrested. However, in spite of the fact that the varices are eradicated, they still have the possibility of complications later as a result of CLD, which include esophageal variceal bleeding and hepatocellular failure leading to hepatic encephalopathy. These patients with CLD need regular follow-up for the management of cirrhosis, including the surveillance for HCC. Unfortunately, some of these patients develop disease rapidly to the extent that the treatment of HCC is not possible. In this study, first two patients had recurrent problems and were not considered for liver transplant. Third patient had single lesion but other factors prevented from referring patient for liver transplantation. Patients who have HCC after transplantation have significant survival advantage. The limitations of study include experience of single centre and limited follow-up period. Longer follow-up may reveal additional cases of cancer.

**CONCLUSION**

Hepatitis C related cirrhosis has potential of carcinogenicity and development of hepatocellular carcinoma. Those patients, who achieved sustained virological response after antiviral therapy, still need long-term follow-up and surveillance for hepatocellular carcinoma. There can be a hope that with long-term follow-up, these patients will have fewer complications of chronic liver disease and may be a candidate for liver transplantation, if hepatocellular carcinoma is detected early with continuous surveillance.

**REFERENCES**

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### References

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