



## Epidemiology and Radiotherapy of Hepatocellular Carcinoma

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### Keywords

Hepatocellular cancer, Epidemiology, Stereotactic, Radiotherapy, Socioeconomic factors

### Background

Hepatocellular carcinoma (HCC) is a primary liver cancer secondary to chronic liver conditions such as hepatitis B virus (HBV) and C virus (HCV) infections, obesity and alcoholism [1-3]. HCC is the sixth most common solid tumor, and third most lethal cancer globally [2]. There may be a gender difference in the development and outcome of chronic liver diseases [4]. In U.S., the incidence of HBV infection has declined since the introduction of HBV vaccination in 1981 [5]. But approximately 350 million of global population has chronic HBV infection [6]. Hepatitis C virus (HCV) infection is another major source of chronic liver disease and cirrhosis [2]. About 3% of world population are infected with HCV [7]. About 20-30% of HCV patients developed cirrhosis after 2-3 decades [7]. Overall, once cirrhosis developed, the incidence of HCC development is 3-4% per year [2]. More than 80% of HCC develops from a cirrhotic liver [2]. The incidence of HCC is rising globally especially in the developing Asian and African countries [1,8]. This paper is a part of a series focusing on using advanced stereotactic radiotherapy in challenging oncologic scenario [9].

### Treatment of Hepatocellular Carcinoma

Staging of HCC is based on Barcelona Clinic Liver Cancer (BCLC) staging system. HCC progresses from stage A to D based on the number of nodules, size, performance status of the patient (symptomatic or not), vascular invasion and extrahepatic spread [2]. Asymptomatic small HCC with good liver function has a cure rate of about 70% [2]. But most HCC (60-70%) are diagnosed at an advanced stage [2]. Development of the first oral agent Sorafenib (Nexavar), a multitargeted tyrosine kinase inhibitor has a small but significant improvement in the survival of advanced stage HCC with good liver function [2].

Treatment of earlier stage HCC includes liver transplant [1], surgical resection, transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and radiotherapy [10-14]. Child-Pugh (CP) liver functional status takes into account five clinical measures total bilirubin, serum albumin, prothrombin time (PT) international normalized ratio (INR), ascites, hepatic encephalopathy. CP score

and BCLC stage are important factors in selecting curative versus non-curative treatment for HCC patients [2].

### Public Health Aspects of Hepatocellular Carcinoma

Prevention of HCC may depend on removing the underlying major risk factors of HCC [15]. For example controlling current obesity epidemic may reduce the risk of Non-alcoholic Fatty Liver Disease (NAFLD) and its most severe form Non-Alcoholic Steato Hepatitis (NASH) and the subsequent development of HCC [15]. HCC is the first human tumor that is amenable to prevention by HBV vaccination [15]. In Taiwan, mass HBV vaccination has led to a decrease in childhood HCC [15]. And the global burden of chronic HBV infection has also decreased because of mass vaccination since early 1980s as a child may prevent this [15]. However, HBV vaccination may not be available in some developing countries. In Canada, it has been found that it is cost effective to screen and vaccinate their newly arrived immigrants [6]. Screening for HCV infection may also be cost effective [16]. Although there is no currently no HCV vaccine available [16]. HCC surveillance by liver ultrasound every 6 months may be cost effective in detecting HCC early in high-risk population [17,18]. Early detection of HCC may increase the likelihood of having curative and effective treatments [17].

In U.S., Center of Disease Control (CDC) National Health and Nutrition, Examination and Survey (NHANES) collected data of HBV and HCV infection and their other health variables including mortality data [19,20]. National Cancer Institute (NCI) Surveillance, End Results and Epidemiology (SEER) project also collects treatment and outcome data on HCC [10]. These are valuable sources of data available for public health research in this area.

### Radiotherapy for HCC

Radiotherapy has become important in the treatment of HCC as a bridge to transplant and for palliation, especially stereotactic body radiotherapy (SBRT) and proton beam radiotherapy are considered effective treatments [13,21,22]. Radiotherapy is particularly useful for HCC patients with venous thrombosis that may be a contraindication for other local therapies [23-25]. The local control rate could be as high as 90% for small HCC less than 3 cm [26]. Local control of HCC has been associated with improved survival [12,27]. Local therapy has been found to be useful for patients to meet the Milan Criteria (HCC < 5 cm, or up to 3 HCC, each < 3 cm) on transplant list for more than 6 months [26,28]. But it may be controversial for patients on a shorter waiting list for liver transplant [26].

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Advanced radiotherapy technology is critical in the success of radiation treatment of HCC [13,29-31]. However, most of the hospitals in the countries where HCC is most prevalent may not have the appropriate technology to deliver good radiotherapy for HCC patients [32]. Even in advanced countries such as U.S. socio-economic factors could still be a barrier to access to these advanced technologies. Studies related to the socio-economic barriers facing HCC patients may help to solve these problems and help them achieve best and most cost effective radiation treatment outcome.

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