

DRAFT

Working Group 10. Liver Cancer

Introduction & Background

Liver cancer can refer to a variety of malignant diseases that are either primary or secondary to the liver. Primary liver cancers include hepatocellular carcinoma (HCC), cholangiocarcinoma, hepatoblastoma, fibrolamellar carcinoma, angiosarcoma, and several other rarer forms. The liver is also a frequent site for secondary tumors that have metastasized, most frequently from colorectal, breast and gastric cancers. The term “liver cancer,” both generally and in this document, refers to malignancies that are primary to the liver. HCC comprises more than 80% of primary liver cancers in most countries. Concern about HCC has been growing recently, due to the recognition of the magnitude of the problem in many developing countries and because of the striking increase in its incidence in the U.S. and other developed, western countries in recent years. The incidence of HCC has doubled over the last two decades in the U.S. This chapter focuses on the problem of HCC.

It is estimated that 10,000 to 12,000 new cases of HCC occur each year in the U.S. In some parts of the world, such as China, Southeast Asia, and sub-Saharan Africa, HCC is the most common form of internal malignancy and the most important cause of cancer-related mortality. In high-incidence areas of Asia, rates of HCC range from ~20 to as high as 100 per 100,000 population. Worldwide, it is estimated that about 600,000 new cases of primary liver cancer (HCC and cholangiocarcinoma) occur each year, with two thirds of cases in men and a third in women, amounting to approximately 5.6% of all human cancers.

A striking feature of HCC is that it occurs largely in the context of known risk factors. This makes HCC almost unique among cancers because the underlying cause in individual patients can often be identified, in contrast to most other major cancers, for which risk factors can be identified only at a population level. At least 80% of cases occur in patients with chronic liver disease and cirrhosis. The major causes of cirrhosis and HCC include hepatitis B, hepatitis C, alcoholic and nonalcoholic fatty liver disease, hemochromatosis, and alpha-1-antitrypsin deficiency. In some cases, the cause for the cirrhosis is unknown (“cryptogenic”). However, HCC is not always accompanied by cirrhosis, indicating that disease factors other than fibrogenesis and cirrhosis are also important. In the U.S., Europe, and Japan, the major cause of HCC appears to be hepatitis C, whereas in China, Southeast Asia, and Africa, the major cause is hepatitis B. The rising frequency of HCC in the U.S. in recent years has been attributed largely to chronic hepatitis C, as a consequence of the epidemic of this disease that occurred in the 1960s to 1980s.

HCC is a highly fatal cancer with a median survival time from the date of diagnosis of 7 to 8 months. The only potentially curative therapies are resection and liver transplantation, and few effective therapeutic options exist for advanced cases. The fact that individuals with chronic viral hepatitis who are at risk for liver cancer can be readily identified makes HCC an attractive disease for developing strategies for early detection or prevention. Yet, even with regular surveillance, HCC is often too advanced for local resection or transplantation. Furthermore, the

therapeutic potential of hepatic resection and tumor ablation for patients with HCC is limited by the fact that most patients also have underlying cirrhosis and, therefore, cannot tolerate large liver resections. Even with successful resection, recurrence or *de novo* reappearance of HCC is common. In recent years, liver transplantation has been increasingly used as the primary means of managing HCC. With the rising rate of HCC in the U.S., this tumor threatens to place an increasing burden on the allocation of livers for transplant.

Recent Research Advances

Although the link between HCC and cirrhosis has been known for many years, the association between HCC and infection with the hepatitis B virus (HBV) was first identified in the early 1970s. The association between HCC and the hepatitis C virus (HCV) became obvious very soon after the discovery of this viral agent in 1989. More recently, there is growing evidence linking HCC with obesity, diabetes, and insulin resistance factors that are involved in the development of nonalcoholic steatohepatitis (NASH).

The mechanisms by which chronic liver disease results in HCC are not clearly understood. In many cases, it appears that cirrhosis represents the key mediator. Thus, diseases such as chronic hepatitis C, alcoholism, hemochromatosis, and alpha-1-antitrypsin deficiency first cause cirrhosis, after which HCC often arises. Hepatocyte populations of most cirrhotic nodules recently have been found to be monoclonal, and they proliferate repeatedly, which makes them susceptible to the development and propagation of genetic lesions. The discovery that the DNA genome of HBV could integrate into host chromosomes, and that this genetic integration could be found in HCC tissue, suggested that HBV might cause cancer through insertional mutagenesis, a process already well-described in retroviruses. Although subsequent research has not yet generated a unifying mechanism by which HBV DNA integration leads to HCC, recent research with gene expression and deletion arrays has revived this hypothesis.

Analysis of animal models of hepatocarcinogenesis has identified hepatocellular lesions that precede the emergence of HCC, and similar preneoplastic lesions have recently been detected in livers of humans. This discovery provided the basis for investigating, and ultimately identifying, the genetic alterations and molecular pathways that initiate hepatocarcinogenesis in humans. Although there are many small animal models of chemical hepatocarcinogenesis, no useful small animal models of HBV- and HCV-related hepatocarcinogenesis exist. However, the processes of HBV- and HCV-related hepatocarcinogenesis have been partially modeled in transgenic mice that express portions of the viral genome in hepatocytes. Furthermore, woodchucks chronically infected with the woodchuck hepatitis virus (WHV, a hepadnavirus similar to human HBV) almost universally develop HCC, and this model may be exploited to study the human disease. Further study of animal models of HCC using new technologies of genomic analysis may identify genetic defects that activate or suppress specific molecular pathways that lead to HCC.

The last decade has brought tremendous advances in the diagnosis and treatment of HCC. Body imaging with computed tomography (CT) and magnetic resonance imaging (MRI) can now reliably detect the increased vascularity associated with early HCC. For years, the mainstay of treatment of HCC has been surgical resection, although only a very small proportion of patients

is eligible at presentation for this potentially curative surgery. More recently, studies from Milan, Italy have shown that liver transplantation is highly successful in providing long-term survival in selected patients. These studies are the basis for the “Milan Criteria,” which are used as guidelines to qualify HCC patients for liver transplantation and include the presence of: (1) either a single lesion less than 5 cm or a maximum of 3 lesions with none greater than 3 cm, and (2) no extrahepatic or portal vein involvement. However, the majority of patients with newly diagnosed HCC have tumors that already exceed these criteria and, therefore, are not ideal candidates for transplantation. Recently, local ablative procedures have been performed in patients with unresectable HCC. Transarterial chemoembolization has been shown to modestly increase in survival in selected patients with HCC. New minimally invasive techniques include radiofrequency and thermal ablation, transcatheter alcohol injection, and transarterial internal radiotherapy with yttrium-90 spheres that have been shown to result in significant reduction in the size of HCC, but their efficacy in prolonging survival has yet to be demonstrated.

A triumph of twentieth-century medicine was the introduction of a safe and effective vaccine against HBV. Mass vaccination programs are in place in many countries, and the impact of HBV vaccination on rates of HCC is already measurable in the context of childhood HCC, which has significantly decreased in incidence in Taiwan. Thus, HCC is the first human cancer to be preventable with a vaccine.

Research Goals

The major goal of research on liver cancer is to understand the cellular and molecular mechanisms of hepatocarcinogenesis and to develop means for early detection, treatment, and prevention of HCC.

Basic Research: The major challenge in basic research on HCC is to more completely define the genetic basis of hepatocarcinogenesis and the molecular processes and pathways involved in the malignant transformation of hepatocytes (Matrix Cell C2). Knowledge of the involvement of cancer genes in transformation, including promotion and alteration in the normal patterns of regulation of cell proliferation and death, is key to the understanding of carcinogenesis in the liver. This knowledge is also necessary to identify potential targets for future therapy. Molecular signatures of HCC may best be identified and validated by simultaneously investigating liver lesions of both humans and animal models (Matrix Cell A2). Analysis of genetic and molecular aberrations in transgenic models in mice may provide the most efficient way to first identify key molecular pathways that lead to HCC in humans (Matrix Cell B3). The woodchuck hepatitis virus model, in which virtually all chronically infected animals eventually develop HCC, is an excellent candidate for molecular studies of carcinogenesis and virus-host interactions.

Clinical Investigation: Recent findings suggest that HCC has distinct heterogeneity, in terms of clinical characteristics and rate of growth or invasiveness, as well as “molecular signature.” A specific goal for future research is to further define the molecular signals of human HCC using gene expression arrays and proteomics on liver tissue and correlate these findings with clinical outcome and response to therapy (Matrix Cells A2 and A1). These molecular signatures may

also provide insight into the cellular pathways that are involved aberrantly in liver cancer and identify potential “targets” for the development of specific therapies (Matrix Cell B3).

Another major goal of research is to identify sensitive and specific biomarkers for HCC that appear early in the course of the natural history of this tumor, at a time when curative intervention with surgery or transplantation might be possible. Such biomarkers might be identified using proteomic or gene expression array analyses of tumor tissue or by conducting proteomic or antibody plus phage display studies of serum from patients with HCC (Matrix Cell A2). Once biomarkers are identified, they could be validated in human samples and ultimately subjected to prospective evaluation in high-risk individuals for their ability to improve early diagnosis of HCC and survival (Matrix Cell B2).

Although the majority of cases of HCC arise in patients with cirrhosis due to chronic hepatitis B or C or to alcoholic liver disease, a proportion occur in patients with “cryptogenic” cirrhosis. Some of these cases are believed to represent advanced stages of NASH. An important goal is to gain better information on the incidence of HCC in the U.S., as well as on the specific clinical features and underlying diseases of patients that present with this cancer. These studies could be combined with the development of standardized terms and nomenclature for diagnosis, staging and grading of HCC (Matrix Cell B1). Surveillance and epidemiologic studies on incident cases of HCC would facilitate this effort (Matrix Cell A1). This research, as well as prospective studies in patients with NASH, could also focus on whether nonalcoholic fatty liver disease is a risk factor for HCC and on what features of NASH place patients at highest risk for developing cancer (Matrix Cell B2).

Prevention and Therapy: At the present time, chemotherapy for HCC is unsatisfactory. While several regimens using systemic or locally infused chemotherapy have proven capable of causing tumor shrinkage, none has been shown to improve survival, and many are toxic, with adverse effects on quality of life during the terminal phases of this cancer. A central problem with chemotherapy is that most patients with HCC have an underlying cirrhosis or advanced liver disease, such that tolerance of cytotoxic chemotherapy is poor. Indeed, many patients with HCC die, not as a consequence of the spread of tumor, but rather from complications of the associated chronic liver disease. To enable progress in chemotherapy of HCC, future research on the identification of noncytotoxic drugs for HCC is warranted (Matrix Cell C3). Pursuit of the increasing promise of targeted drug therapy for the treatment of HCC is particularly important because cytotoxic agents are not especially effective. Other potential therapeutic approaches to HCC that might be explored include hormonal manipulation, immunotherapy, and specific inhibition of angiogenesis and growth factors. Development of these potential therapies will rely on basic research in carcinogenesis in general and hepatocarcinogenesis in particular.

Continued reliance on liver transplantation to manage HCC in patients with cirrhosis is limited by the inadequate supply of donor livers. The success and optimal use of liver transplantation is important to evaluate on a continuing basis, particularly because indications and practices related to HCC (e.g., organ allocation policy, tumor size, histologic documentation, use of living donors) change with advancing knowledge. At present, the Milan Criteria are used to define eligibility for transplantation, but the size of the tumor to which the allocation policy applies continues to change. New lesions seen on imaging studies in patients with cirrhosis are often interpreted as

HCC without histological confirmation. However, upon transplantation, many of these new lesions are found to be benign dysplastic nodules rather than HCC. Therefore, better means of specific diagnosis of HCC that do not rely upon liver biopsy or monitoring over time to demonstrate growth would enable the accurate diagnosis of HCC in support of sound application of the transplantation criteria. Such approaches to diagnosis might include functional imaging (Matrix Cell A3) or the use of newer biomarkers.

Therapy for unresectable HCC has barely progressed in the last 10 years. Nevertheless, many promising modes of liver-directed therapy are available, including transarterial chemoembolization, alcohol injection, thermal and radiofrequency ablation, and internal radiotherapy with yttrium-90 spheres. The role of these advanced techniques has yet to be defined (Matrix Cell B1). Using chemoembolization as the standard for treatment, prospective controlled trials could help to clearly define the relative efficacy and safety of other techniques, with particular attention to side effects and quality of life.

Of course, the most important goal for liver cancer research is to develop means of prevention (Matrix Cell C1). Because HCC occurs largely in high-risk individuals, prospective studies are possible. A major effort is focused on therapy of the underlying conditions, such as the use of nucleoside analogues for hepatitis B, peginterferon for hepatitis C, and insulin-sensitizing agents for NASH. In these trials, it is important to focus on whether therapy averts or delays the appearance of long-term complications, such as the development of cirrhosis and HCC. However, even without an effective primary therapy, prospective trials of non-specific chemoprevention of HCC would be beneficial. Such trials might focus on antioxidants, retinoids, cyclooxygenase inhibitors, herbal medications, or other relatively non-toxic compounds.

Steps to Achieve Research Goals

Advances in understanding of the molecular basis of HCC are dependent on the availability of well-characterized samples of cancer and the surrounding noncancerous tissue. Noncancerous liver tissue taken from an area adjacent to HCC is helpful as reference material to identify possible preneoplastic lesions. Tissue from cases of HCC, including both cancerous and adjacent noncancerous tissues, is readily available from liver transplantations performed for HCC, an increasingly common procedure. This resource could be made more available and could be more fully utilized. A national liver tissue bank containing liver cancer tissue, noncancerous/preneoplastic adjacent liver tissue, and nondiseased liver tissue distant from the cancer site, together with serum specimens and closely linked clinical information on these tissue donors, would enable further productive research on the mechanisms of HCC development. The tissue specimens and correlated clinical information contained in such a bank would help to define the roles of different genes and molecular pathways in hepatocarcinogenesis and to identify possible targets for anticancer therapy. The availability of tissue and serum from patients with and without cancer, but who possess common risk factors, will also help to identify biomarkers for HCC. To this end, clinical trials of therapy for liver disease and natural history studies could be more fully utilized for their ability to provide serum and tissue samples before and at the time of development of HCC. Attempts to validate new biomarkers for HCC would

also be greatly facilitated by the availability of serum samples taken from patients at high risk for HCC before the tumor is symptomatic or large enough to be visualized using ultrasound or other imaging methods.

Clinical trials of new therapies for unresectable HCC could be encouraged and compared with more standard therapies such as chemoembolization. These studies would benefit from the use of standardized endpoints for success of therapy and validated instruments for the assessment of quality of life that are specific for this cancer. The formation of cooperative cancer study groups that focus on HCC, similar in scope to those established for lymphoma, breast cancer, and lung cancer, could serve as a means of active surveillance for HCC in the U.S. These groups could also provide focus to promote international collaborations in the area of liver cancer.

Matrix of Research Goals in Liver Cancer

	Short-term Goals (0-3 years)	Intermediate-term Goals (4-6 years)	Long-term Goals (7-10 years)
High Risk	A3. Develop functional imaging techniques that can separate HCC from benign lesions.	B3. Identify target for potential therapy of HCC from molecular studies on human tissue and/or animal models.	C3. Based upon molecular analyses, develop effective, noncytotoxic therapy for HCC.
Intermediate Risk	A2. Identify potential biomarkers for HCC. Define the molecular signatures & heterogeneity of HCC and determine how they correlate with clinical features.	B2. Validate reliability of biomarkers for early detection of HCC. Identify risk factors for HCC associated with NASH.	C2. Define the cellular and molecular pathways that lead to hepatocarcinogenesis.
Low Risk	A1. Establish liver cancer serum & tissue bank. Establish means of active surveillance of HCC in the U.S.	B1. Demonstrate the relative efficacy, safety, & benefits of local ablative therapies for HCC. Develop standardized terms & nomenclature for diagnosis, staging, & grading of HCC.	C1. Demonstrate an effective strategy for prevention of HCC in high-risk populations.