

# Hepatocellular Carcinoma: Current Management and Future Trends

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The hallmarks of hepatocellular carcinoma (HCC) are that it is identified clinically at an advanced stage and usually together with cirrhosis. Surgical resection has been considered the optimal treatment approach, but only a small proportion of patients qualify for surgery, and there is a high rate of recurrence. Approaches to prevent recurrence have included chemoembolization before and neoadjuvant therapy after surgery, neither of which has proven to be beneficial. Liver transplantation has been successful in treating limited-stage HCC, affecting cure of both the tumor and underlying cirrhosis. However, only a minority of patients with HCC qualify for transplantation. Recently, chemoembolization has been shown to prolong survival in selected patients who do not qualify for transplantation or resection. Other innovative, relatively noninvasive local ablative therapies have been introduced and have been shown to be effective in reducing tumor size but not in prolonging survival. Standard chemotherapy is poorly tolerated in patients who do not qualify for resection. Both doxorubicin and cisplatin are frequently used, but overall response rates are low, and neither seems to prolong survival. Prospective, randomized controlled trials using current therapies are needed to better define optimal management of this important tumor. Most needed, however, are new therapeutic agents that are effective against HCC, are noncytotoxic, and are tolerated by the typical patient with underlying cirrhosis. Newly emerging agents with promise include  $^{90}\text{Y}$  microspheres, antiangiogenesis agents, inhibitors of growth factors and their receptors, and K vitamins.

Hepatocellular carcinoma (HCC) is the most common tumor that originates in the liver, and it has great heterogeneity with respect to tumor behavior and disease of the underlying liver.<sup>1</sup> Although most types of cancer are subclassified on the basis of the TNM staging system or the extent of disease, HCC is not a uniform disease within any given current staging system. In addition, it is heterogeneous with regard to the severity of the underlying cirrhosis. The main difficulties regarding evaluation of tumor responses, assignment of severity of disease, and measurement of treatment outcomes in HCC relate to the fact that 80% of patients with HCC have 2 diseases, each of which,

independently, may cause death; namely the cancer and the underlying cirrhosis. Concomitant cirrhosis distinguishes HCC from all other types of cancer, and has been acknowledged in at least 1 staging system, that of Okuda,<sup>2</sup> but confounds and confuses the evaluation of different treatments.

## The Underlying Liver Disease

In most large case series, more than 80% of patients present with HCC that has developed as a consequence of chronic liver disease usually, but not always, in association with cirrhosis. Exceptions include chronic HBV infection and certain HCCs in sub-Saharan Africa, where aggressive and massive tumors can develop before the onset of cirrhosis. In contrast, HCC that develops in association with HCV infection usually arises in patients with underlying cirrhosis, and the incidence of HCC is greater with worsening stages of cirrhosis. The published figures for the development of HCV-related HCC are somewhat variable. However, it seems that among approximately 3 million carriers of HCV in the United States, cirrhosis will develop in 20%–30%, and of those, HCC will likely develop in 3%–5% per year. There may be differences in the character of HCC based on the underlying liver disease. For example, patients in China with HBV-associated cirrhosis not uncommonly present with large, single tumors and little portal vein thrombosis, whereas patients with HCV-associated cirrhosis more commonly present with multifocal HCC that invades the portal vein.

There are well-documented gender differences in the incidence of HCC with a male predominance, varying in ratio from 3:1 to 9:1,<sup>1</sup> but only in the presence of cirrhosis. The gender differences are not as marked in countries where there is little chronic hepatitis. The causes of the gender differences have not been estab-

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*Abbreviations used in this paper:* CT, computerized tomography; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

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lished, although endocrine control of carcinogen metabolism has been suggested.

The severity of the underlying cirrhosis has a profound effect on all treatment decisions and limits all treatment modalities except liver transplantations. The presence of cirrhosis limits the extent of any planned hepatic resection because the residual liver must be able to tolerate volume loss and be able to regenerate. Cirrhosis also limits both systemic and hepatic artery chemotherapy (transarterial chemotherapy or transarterial chemoembolization [TACE]) because the agents are all cytotoxic and can cause further liver injury. Injury from chemotherapy is readily tolerated by the normal liver, but is often not tolerated by the liver that has already been chronically damaged as a result of disease. The only treatment modality that is not influenced by the severity of cirrhosis is liver transplantation, which alone is capable of curing both diseases at the same time.

### HCC Characteristics

Evidence from computerized tomographic (CT) scans, liver transplants, recurrence rates after resection, and animal hepatocarcinogenesis models have shown that HCC tends to be a whole-organ disease, is usually multifocal, is often bilobar, and has 2 characteristic vascular abnormalities. The first is neovascularity, in which small branches of the hepatic artery grow and supply the growing tumor (tumor neovascularity). New hepatic arterial growth is likely required for HCC to develop beyond a certain size. This arterial neovascularity is entirely plastic and regresses in response to successful chemotherapy. The neovascularity is readily apparent on hepatic angiography and provides the characteristic appearance on fast, triple-phase CT scanning, in which the initial rapid arterial bolus reveals a vascular blush, distinguishing HCC from most, although not all, metastatic tumors to the liver (exceptions are metastases from breast, thyroid, and renal cancers). Secondly, a distinctive vascular characteristic of HCC is its propensity to invade the otherwise normal portal veins. This is seen histologically as tumor cells growing into the portal vasculature and on CT scanning, by thrombosis, expansion, and often arterialization of the invaded portal vein, typically the right or left main branch but also the main trunk portal vein. Portal vein involvement is, after metastasis, the most important negative predictor of prognosis<sup>3</sup> because it may be the main route through which metastases occur.

In a large series of patients with HCC from the University of Pittsburgh,<sup>1,3</sup> metastasis occurred in 40% of patients. However, metastases do not play as predominant a role in survival and patient management in HCC as with most

other tumors. The reason for this is that the major growth of HCC tends to be confined to the liver, and most patients die as a result of liver failure or local growth of the tumor.<sup>4</sup> Although regional lymphadenopathy is commonly seen on CT scans of patients with HCC, its significance is frequently unclear, because regional lymphadenopathy can be the result of either cirrhosis or HCC, and the lymph nodes themselves are often not sampled. Further, in transplantation patients, they contain cancer in only 10% of cases.

### Biopsy

The role of biopsy for proof of diagnosis of HCC has been the subject of controversy. For almost all other types of cancer, a biopsy and histologic confirmation are considered mandatory before making a diagnosis and starting therapy. Because of occasional tumor seeding from the needle track during biopsy evaluation of HCC, it has been proposed that biopsy be avoided. However, hepatic imaging and serum testing for tumor markers of HCC are not always reliable, and the absence of biopsy confirmation of diagnosis may account for excellent survival reported in some series. In patients with cirrhosis, regenerating nodules can closely resemble HCC on imaging tests, and  $\alpha$ -fetoprotein levels can be elevated because of disease activity even without HCC. Conversely, it is only elevated in 50% of HCC patients. A recent consensus meeting in Europe recommended that the diagnosis of HCC could be made based solely on the presence of a vascular tumor identified in a person with cirrhosis and an increasing level of  $\alpha$ -fetoprotein.<sup>5</sup> This approach is reasonable, but is not without errors. Serum  $\alpha$ -fetoprotein testing, in particular, is inaccurate in patients with cirrhosis. With the advent and increasing knowledge of the discipline of molecular biology, it is likely that new and more accurate markers will be identified using proteomic and genomic profiling.<sup>6</sup> For the present, however, the possible risks against the benefits of histologic diagnosis must be weighed in deciding whether to obtain biopsy confirmation of the diagnosis of HCC. At the University of Pittsburgh, where it is routine practice to obtain biopsy confirmation of HCC, over 1500 biopsies have been obtained with carcinomatous tracking in the needle path developing in only 5 cases ( $\sim 0.3\%$ ). All local recurrences were treatable by resection or external beam radiation.

Future genomic profiling of HCC may make biopsy confirmation and characterization more important. In therapy of breast cancer, for instance, treatment is guided by the determination of estrogen or progesterone receptor or HER-2 status performed on the biopsy specimen. Similar characterization of HCC gene expression profiles

may soon be important. Thus, at present, biopsy of HCC is a rational approach to management, particularly because most therapies are invasive and potentially harmful, except when there are specific contraindications or shortcomings, as with severe ascites or a mass lesion in an inaccessible position.

### **HCC in the United States**

The experience with HCC at the Liver Cancer Center of the University of Pittsburgh recently has been summarized.<sup>1,4</sup> During a 15-year period, 1700 patients with HCC were evaluated. Seventy-five percent of patients had bilobar cancer, 72% had portal vein thrombosis, and 65% had 3 or more tumor masses in their livers. Thirty percent had HCV infection, 20% were infected with HBV, and 28% had alcohol-associated cirrhosis. Among those with HCV infection, more than 66% also had a history of alcoholism. Interestingly, 20% of the patients had no identifiable underlying liver disease. The male-to-female ratio was 2.5:1. The ages of the patients averaged 56 years and ranged from 6 months to 92 years. Twenty percent presented with end-stage liver disease and were not eligible for any form of treatment. The median survival in these untreatable patients was 3 months, in keeping with the known rate of survival of HCC.

### **Treatments for HCC**

A high proportion of patients with HCC in the United States do not receive any therapy. The exact proportion is not known, but may be as high as 50%. There are several reasons for this low rate of therapy. Chronic liver disease is often silent, and many patients are unaware of having liver disease or being at risk for liver cancer. Furthermore, among those patients who are known to have liver disease, there are no guidelines or accepted approaches to regular surveillance. As a consequence, most patients with HCC rarely present with symptoms unless there is advanced-stage cancer. Because the cancers are large, they are often bilobar or have already invaded a major trunk of the portal vein, and hence are not resectable. Because of the late stage of presentation, many patients with HCC are not referred to a medical oncologist for either systemic chemotherapy or TACE, although a number of them may be responsive to such treatments. The lack of referral for chemotherapy reflects an atmosphere of nihilism over therapy for this tumor, and until recently, a lack of new and innovative therapies. Finally, contraindications to therapy may already be present (ascites, end-stage liver disease) and referral is considered unjustified.

### **Surgical Resection**

Surgical resection of varying degrees and extent has been time-honored standard treatment for HCC.<sup>1,3,7</sup> Recent series, particularly from Asia, suggest that in experienced hands, perioperative mortality can be less than 5%. Although recurrence rates after surgery have decreased and survival has increased over the last 20 years, most patients with TNM stage II still have only a 50% 5-year survival, death usually being caused by recurrent cancer.

### **Other Ablative Localized Treatments**

An increasing array of other localized semisurgical treatments has become widely accepted for extremely localized tumors. These include percutaneous ethanol injection, radiofrequency ablation, cryotherapy, and newer forms of radio-wave therapy. These local ablative therapies seem to be similar in applicability, and results are highly dependent on clinician skills and choice of patients. Local ablative therapies are generally useful for patients with 1 or 2 tumor lesions with a maximum diameter of 3 cm.

### **Liver Transplantation**

There were 2 hopes for liver transplantation in the management of patients with advanced HCC. The first was to remove the limitations that cirrhosis imposes on the surgeon to resect HCC. The second was to improve the ability of the surgeon to resect larger tumors. In the first category, liver transplantation has been gratifyingly successful, and HCCs that are confined to the liver can be surgically removed, whatever the degree or severity of the underlying cirrhosis.<sup>3,7</sup> For the second, there continues to be a learning phase on how to use and extend the possibilities of liver transplantation for the management of advanced-stage HCC. It is now accepted that patients with small tumors who fulfill the Milan criteria—1 tumor less than 5 cm or up to 3 tumors all less than 3 cm—seem to survive as well after liver transplantation, as do patients transplanted for end-stage liver disease without HCC.<sup>5</sup> Nevertheless, too much caution may have been exercised in not extending liver transplantation to patients with larger tumors or with larger numbers of tumors without portal venous thrombosis. What is really needed is not a static anatomic description of the extent of the HCC, but more sophisticated prognosticators of the behavior of an individual tumor, which probably can only come from molecular markers or proteomic profiling.

Even in the initial 2 large series of reports of liver transplantation for HCC,<sup>3,7</sup> 20% of patients with stage IV HCC had 5-year survivals. At present, there are no means of identifying, before transplantation, which pa-

tients will do well and which will not. Furthermore, there has never been a randomized controlled trial to evaluate the benefits of ablative therapies directed at downstaging the tumor before liver transplantation compared with transplantation alone. Multidisciplinary approaches to cancer have been highly successful in cancers of the breast, head and neck, and colon; similar combinations of approaches using chemotherapy and surgery or transplantation are appropriate also for liver cancer and should be pursued in multicenter randomized controlled trials. In addition, the standards for acceptance of liver transplantation for HCC need to be continually reviewed and reconsidered. In other types of advanced cancer, a 50% 5-year survival rate is considered worthwhile, but in liver transplantation, a 50% 5-year survival is not. For most patients with advanced HCC, extension of life for 3 years would be considered meaningful if the quality of life were reasonable.

### Hormonal Therapy

Almost 90% of newly diagnosed HCCs referred to the University of Pittsburgh were considered to be non-resectable and nontransplantable as judged by the extent of the tumor.<sup>1</sup> The management of such tumors is currently nonsurgical. The gender differences noted in HCC incidence rates have encouraged many investigators to examine tumor profiles for hormonal or growth factor receptors and, with or without this information, to embark on clinical trials of various hormonal modalities, including agents such as tamoxifen to inhibit estrogen actions (which is unlikely to be successful because this tumor predominantly occurs in male subjects) and anti-androgens such as leuprolide acetate and flutamide.<sup>1</sup> Despite many trials, the overall results have been disappointing and survival has remained poor. Nevertheless, such approaches are attractive because the agents are in general nontoxic, inexpensive, and easy to administer.

### Chemotherapy

A huge number of randomized and nonrandomized clinical trials to evaluate the usefulness of single agents or combinations of agents of cytotoxic cancer chemotherapy have been published and recently reviewed.<sup>1,8-10</sup> Overall, few published series have been able to show response rates in >20% of the patients (considered to be a lower limit of usefulness for most cancers), and very few claims have been made for prolonging survival. Some more recent combinations such as cisplatin, interferon  $\alpha$ , Adriamycin, and 5-fluorouracil are extremely toxic and yield response rates of only 20%, and show no survival advantage compared with supportive care alone.<sup>11</sup>

Higher concentrations of cancer chemotherapeutic agents can be delivered directly to the HCC via the hepatic arterial route. Considering that this is the major vascular supply of these tumors, an even larger number of papers have reported experience of hepatic artery chemotherapy or hepatic artery chemoembolization (TACE) with single agents, a dizzying combination of agents, and at doses that are not replicated by any 2 institutions. The nature of the embolizing agents also varies dramatically from site to site, the most common agents being lipiodol (Ethiodol) or Gelfoam (gelatin sponge particles that are cut with scissors and then autoclaved). Despite huge efforts in this area from multiple institutions, the effect on survival has been difficult to prove.<sup>1,4,8,10</sup> This has started to change with the recent publication of 2 trials, 1 from Spain<sup>12</sup> and the other from Hong Kong,<sup>13</sup> showing a survival advantage for TACE using either doxorubicin (Adriamycin) or cisplatin with embolization, compared with supportive care only. Both of these trials showed a survival benefit, but both also had limitations. Nevertheless, this approach has set a new standard with which other agents or combinations of treatments should be compared, because for the first time, both have shown a survival advantage for unresectable HCC using TACE.

## Future Directions in Therapy of HCC

### A. Resection

The major shortcoming of hepatic resection for HCC is the high rate of recurrence, and future studies should be directed at decreasing recurrences. The high recurrence rates for stages II and III HCC postresection have led to attempts by investigators to decrease these rates with agents that have known activity against HCC. These agents have included neoadjuvant chemotherapy to downsize the tumor before resection, and postresection treatments to deal with the microscopic disease that may be present in the nonresected portions of the liver. Recently, both postresection <sup>131</sup>I-lipiodol and TACE have been shown in controlled clinical trials to achieve this outcome.<sup>14,15</sup> Thus, TACE or hepatic artery chemotherapy (which may be safer) seem to be reasonable approaches. Although many other agents have been studied for this purpose, they have often been given at subtherapeutic doses. Less toxic or nontoxic agents would be particularly attractive in this setting. Such approaches include the use of vitamin K2 and its analogs (currently in clinical trials for adjuvant effect), <sup>90</sup>Y-microspheres (Theraspheres or Sirspheres) and anti-inflammatory agents such as Cox-2 inhibitors.

## B. Liver Transplantation

Major challenges in liver transplantation for HCC include decreasing the rates of tumor recurrence and pretransplantation downsizing of tumors to achieve the current criteria (Milan criteria) for transplantation and to prevent recurrences. Several noncontrolled or pilot randomized studies have shown that either neoadjuvant or adjuvant chemotherapy administered to subjects with advanced but locoregional HCC in the absence of portal vein thrombosis can be associated with prolonged survival. It is now appropriate to test the efficacy of chemotherapy in this setting in prospective, rigorously controlled randomized trials. Chemotherapy and chemoembolization in preparation of liver transplantation may not be beneficial and may be harmful. The delay imposed on liver transplantation by administration of neoadjuvant TACE in attempting to downstage larger or multiple tumors may adversely affect survival. Conversely, it may decrease recurrences by selecting patients with nonmetastasizing HCCs for transplantation. Continued expansion of criteria for transplantation for HCC places an increased burden on the availability of donor organs, and thus a better understanding of HCC behavior through the use of prognostic markers, such as might be shown by microarrays,<sup>16–19</sup> could be most helpful. Identification of prognostic markers<sup>20–23</sup> would also allow a more rational basis for patient selection for transplantation as well as resection. Furthermore, several assays have been published to detect circulating micrometastases<sup>24</sup> that are associated with high recurrence rates posttransplantation.

## C. Medical Therapy

The ideal chemotherapeutic agent for HCC would be both effective against the tumor and nontoxic to the cirrhotic liver. Few agents exist that meet these criteria. Furthermore, the measures of effectiveness are often made in vitro or in animal models, and the optimal dose for tumor response in HCC in humans for any chemotherapeutic drug is rarely known, especially in the presence of cirrhosis. The 2 most widely used chemotherapeutic drugs for HCC are doxorubicin and cisplatin. Overall, cisplatin seems to be better tolerated in patients with cirrhosis and has less myelosuppressive activity. A dose of 125 mg/m<sup>2</sup> given by hepatic arterial injection is tolerated by the majority of patients presenting without liver decompensation, gross ascites, and a bilirubin of <1.8 mg/dL.<sup>4</sup> With aggressive hydration, triple antiemetics and the use of sodium thiosulfate, nephrotoxicity, neurotoxicity, and ototoxicity can be avoided. Frustratingly, even with standard oncologic tumor partial responses, which mean a decrease by 50% or more of the product of 2 perpendicular diameters of an index lesion, survival at 2 years still does not exceed 40%.

The lack of effect on survival may be caused by loss of control of tumor growth, but is more usually caused by liver failure.

At present, there is no general agreement on an ideal agent or regimen for chemoembolization. The usual practice is to focus treatment on one lobe of the liver at each treatment session, regardless of the extent or number of tumors. Embolizing agents are given to slow vascular flow of the feeding lobar hepatic artery (or branch vessel) and thus increase hepatic extraction of the chemotherapy drug, rather than actually occluding or embolizing the vessel. This practice seems to diminish hepatotoxicity from the embolization. Randomized, controlled trials are clearly needed to establish confidence in the use of TACE for the treatment of unresectable (and untransplantable) HCC. However, the following issues need to be resolved.

**1. Selection of a standard chemotherapeutic and/or embolizing agent, and the optimal dose and dose regimen.** Recently, several new products for chemoembolization, such as biospheres (Embospheres), have been introduced to the market in a defined range of sizes, such as 40–120, 100–300, 300–500, and >500  $\mu\text{m}$  in diameter. The optimal size for embolization of HCC has yet to be established. Also unclear is the optimal frequency of TACE, bearing in mind that standard systemic chemotherapy is given in regular cycles at 4–6-week intervals. With HCC, the oncologist must balance the need for more frequent chemotherapy to enhance the tumoricidal effect with less frequent chemotherapy to permit the liver to recover from the hepatic injury.

**2. Evaluation of responses.** Systemic chemotherapy for most other types of solid tumors in adults is assessed by measuring the decrease in tumor size on CT scan or other imaging modality, or by measuring the levels of a tumor marker, if one exists (such as for prostate cancer or dysgerminomas).  $\alpha$ -Fetoprotein has been used as a tumor marker for HCC, but it is elevated at baseline in only 50% of patients. In addition, the presence of cirrhosis may obscure or prevent the shrinkage or involution of the necrotic tumor so that the accepted parameters of tumor response are not always available. Almost all HCCs are vascular, as judged by the tumor image intensity on the initial, first-arterial-phase bolus of a triple-phase CT scan. A decrease in vascular response has also been considered to be characteristic of HCC response to therapy.<sup>25</sup> However, there has been no established algorithm or even a semiquantitative grading system for tumor vascularity on CT scan or angiogram. In part, this is because of the poor optics in angiography, the heterogeneity of vascular flow in large tumors, and the variability of CT scanning in the location of the slices and the speed of the arterial phase dye bolus. Alternative

indices of tumor response that are growing in acceptance have included time to progression—because a failure of the tumor to grow and act like a cancer is also considered a desirable outcome—as well as evaluation of health-related quality of life.<sup>26,27</sup> Because length of survival is paramount from a patient perspective, even disease stability for patients with HCC is a desirable end point if it translates into enhanced survival. However, all of the parameters should be balanced against quality of life. Assessment of quality of life during cancer treatments is becoming increasingly accepted as a standard part of treatment evaluation.

**3. Patient selection for clinical trials.** Many chemotherapy trials for HCC have a generous range of criteria for patient inclusion, often including those in marginal liver failure. To truly evaluate the anti-HCC activity of a new agent or treatment, only patients with compensated cirrhosis (Child class A) or no cirrhosis should be selected for enrollment. Inclusion of patients with more advanced liver disease will merely confound the survival results because of deaths from progressive liver disease, which may be unrelated to the HCC or its therapy.

#### D. New Medical Agents

Several new classes of nonsurgical therapy for HCC have begun to be evaluated systematically in the past 2 years. These include the following.

1. **Antiangiogenesis** agents, such as vascular endothelial growth factor (VEGF) antibody, angiostatin, and endostatin; thalidomide<sup>28</sup>; thrombospondin analogs; and interferon- $\alpha$ . The vascularity of HCC makes it an excellent candidate for the action of these agents.
2. **Inhibitors of growth-factor-signaling and cell-cycle enzymes**, such as inhibitors of Raf kinase (Bay 43-9006), Cdks, tyrosine kinases, epidermal growth factor receptor antagonists (Iressa), P13 kinase and phosphatase and tensin (PTEN) pathways, mitogen activated protein (MAP) kinase pathway, and suramin.
3. **Nonspecific growth inhibitory agents**, including Sandostatin<sup>29</sup> and arsenic trioxide and activators of apoptosis.<sup>30,31</sup>
4. **Novel means of delivering localized radiation**, such as <sup>90</sup>Yttrium microspheres, Theraspheres, and Sirspheres.<sup>32–36</sup>
5. **Specific antagonists of HCC tumor markers**, such as vitamin K2<sup>37–39,40</sup> and the Cdc25-antagonizing vitamin K analogs.<sup>37,41–43</sup>
6. **Anti-inflammatory agents** that might interfere

with the carcinogenic process, such as Cox-2 inhibitors (celecoxib, rofecoxib).<sup>44–46</sup>

### Conclusions

The largest impact on mortality from HCC will clearly come initially from primary prevention such as decreasing alcohol consumption, decreasing HCV infection through lifestyle changes, improving screening of blood donors, and vaccination against HBV. Next will be the benefit derived from earlier diagnosis leading to more effective therapy for more limited-stage disease. However, new therapies for HCC will continue to be needed. Multiple new therapies are now being evaluated, and combinations of modalities clearly should be examined to improve the efficacy of treatment of most patients who continue to present with an advanced stage of their tumor.

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