
Preface to the Third Edition

In the interval between the second edition of this book in 2009 and this new, third edition, there have been immense advances in both the science and the clinical practice of hepatocellular carcinoma (HCC). The advances are already being built upon to enlarge our understanding of this complex and heterogeneous disease, which is increasing in some parts of the world and decreasing in others. As a result, the original chapters have been updated and more than a dozen new chapters were added, on the following topics: molecular profiling, molecular mechanisms in hepatocarcinogenesis, genomic phenotypes, miRNAs, gene signatures of risk factors, gut microbiota, microenvironment, tumor heterogeneity, circulating tumor cells, immune system and therapy, inflammation, obesity and NASH, staging systems, CT and bioenergetics. Many of the previous chapters have been completely rewritten, including those on local ablation, resection, transplantation, and the final summary chapter. The general scope of these advances is as follows:

1. The introduction into clinical practice of FDA-approved and effective drugs for HCV, with sustained virological responses obtainable for both HBV and HCV, together with high cure rates for HCV.
2. Initial clinical studies showing that the high tumor recurrence rates postresection can be reduced, not by anti-tumor therapy but, by treating underlying virus hepatitis. If confirmed, they will have major conceptual implications for our ideas about HCC therapy and antiviral therapy will be viewed as part of HCC therapy.
3. The underlying cirrhosis (non-HCC part of the liver) is increasingly being seen as not just a comorbid disease (although it is), but also as a source of prognostic information and determinant of HCC biology. Like items #1 and 2, it indicates that the microenvironment is a source of many HCC influences, including immunological, inflammatory, neovascular, cytokine and growth factor actions.
4. Systemic inflammation has become an important and independent prognosticator for many tumor types, including HCC and the simple 2-parameter Glasgow score and its variations are incorporated into clinical practice.
5. Molecular profiling is being used to identify HCC phenotypes, lineage subsets and hopefully, will support rational therapy selection (for example, Met-expressing tumors for Met inhibitor therapies). Furthermore, the increasing commercial availability of kits for purifying tumor cells or free tumor DNA in the blood circulation may provide a safe way of obtaining specific HCC information without the hazards of biopsy, as well as an easy and safe way to provide samples for molecular profiling at various phases of the HCC clinical course in the same patient.
6. Immune checkpoint inhibitors are taking center stage for therapy of many cancer types, with promising early results in HCC.
7. Extended criteria for transplanting larger HCCs and identification of prognostic subtypes are gaining traction.
8. ⁹⁰Yttrium microspheres regional therapy is being recognized as a safer alternative to TACE in the presence of portal vein invasion.

9. Several large phase III trials of new non-sorafenib (multi-)kinase inhibitors failed to meet their expected goals. However, many new targeted agents are currently being evaluated in clinical trials. Furthermore, trials are in progress that examine the combinations of either targeted therapies such as sorafenib with regional therapies (TACE or ⁹⁰Yttrium microspheres), or two or more therapies that target different pathways. In addition, ways of enhancing sorafenib effects or decreasing resistance to its actions are under investigation.
10. We are seeing the development of drugs against new, nongrowth signaling targets, including putative tumor stem cells, dendritic cells, tumor invasiveness proteins, growth-antagonizing microRNAs; the development of tumor vaccines and novel nuclides for internal radiation, such as ¹⁶⁶Holmium and ¹⁸⁸Rhenium, intensity modulated radiation and proton beam therapy.
11. There is a considerable increase in obesity-associated HCC and its different pathogenesis from virus-mediated HCC. This may supplant hepatitis as a cause of HCC in the Western world. The interplay of several factors in many HCC patients, such as HBV and alcohol, HBV and aflatoxin B₁ dietary exposure.
12. There has been a proliferation of proposed staging systems from several countries. Some systems are seemingly more applicable to patients in certain regions of the world than other systems.
13. The sorafenib phase III SHARP trial highlighted the discrepancy between tumor responses and patient survival, as shown by the minimal number of partial objective tumor responses (tumor size change) on the one hand and the finding of significant sorafenib survival benefits on the other. This has consequences for our thinking about the relevance of tumor size change in HCC (especially mediated by cytotoxic chemotherapy) and how we assess useful clinical endpoints for future HCC therapy trials. One result is a reconsideration of the value of 'stable disease' as a desirable endpoint in HCC management.
14. The pace of discovery is quickening, as is the interplay of the basic science and clinical applications. Perhaps the most profound changes have resulted from the availability of an effective vaccine against HBV or primary prevention (though not yet against HCV), and the new effective treatments for both HBV (non-curative) and HCV (curative). Thus, primary, secondary, and tertiary prevention are now available: primary prevention, by vaccination (HBV only); secondary prevention, by treatment of chronic carriers and decreasing the probability of developing cirrhosis and subsequent HCC; and tertiary prevention, by anti-hepatitis therapy resulting in the suppression or eradication of the hepatitis infection, with resultant decreases in postresection HCC recurrences.

Thus, the most significant recent translational advance has been in the area of hepatitis prevention (HBV) and treatment (HBV and HCV), with profound effects on the incidence and likely the biology of HCC caused by hepatitis B or C.

The book is divided into three parts: I, Causes, Biological and molecular basis; II, Diagnosis; III, Therapies. The final chapter provides an overview of current therapy.

Preface to the Second Edition

*You are not obliged to complete the task,
Nor are you free to stop trying.*

—Talmud, Avot

Hepatocellular carcinoma (HCC) used to be regarded as a rare disease. The increasing numbers of chronic HCV carriers in the USA and subsequent increased incidence of HCC seen in most large medical centers mean that it is no longer an uncommon disease for gastroenterologists or oncologists to encounter, and its incidence and epidemiology are changing (new chapter). This has been enhanced by the appreciation that obesity (NASH or NAFL)-associated cirrhosis is also a cause of HCC, as are many metabolic syndromes (new chapter), in addition to carcinogens in the environment (new chapter), hepatitis B (new chapter), and hepatitis C (new chapter). Associated with this has been a clearer understanding of the many mechanisms involved in carcinogenesis of the liver (new chapter). During the period when liver resection and systemic chemotherapy were the only real therapeutic modalities available, the outcomes were generally dismal, especially since most patients presented with advanced-stage tumors. Several recent factors seem to have changed this. They include the more frequent use of aggressive surveillance by ultrasound and CT scanning in patients who have chronic hepatitis or cirrhosis from any cause and thus are known to be at risk for subsequent development of HCC in order to detect tumors at an earlier and thus more treatable stage. Advances in CT scanning, particularly the introduction of multihead fast helical scans, mean that these vascular tumors can often be detected at an earlier stage or multiple lesions can now be appreciated, when only large single lesions were formally seen, so that unnecessary resections are not performed. Helical CTs have also largely replaced the more invasive CT arteriography. Furthermore, advances in MRI scanning (new chapter) have started to measure changes in tumor blood flow as a result of anti-angiogenic therapies (new chapter); so has dye-enhanced ultrasonography (new chapter). Liver transplantation has had a profound effect on the therapeutic landscape. There have always been two hopes for this modality, namely to eliminate cirrhosis as a limiting factor for surgical resection and also to extend the ability of the surgeon to remove ever-larger tumors confined to the liver. The organ shortage for patients with HCC who could be transplanted has been alleviated in part by two new factors. They are the MELD criteria, which give extra points to patients with small tumors, and the introduction of live donor transplants (new chapter), which obviate the need for long waits for a cadaveric donor. Regional chemotherapy and hepatic artery chemoembolization have been around for a long time and have been practiced mainly in the Far East and in Europe. There has not been a consensus on which drug or drug combinations are best or even whether embolization is important, and if so, what type and size of embolizing particle might be optimal. While there is still no consensus on these matters, it has recently become clear from two randomized controlled clinical trials that hepatic artery chemoembolization for unresectable, nonmetastatic HCC seems to bestow a survival advantage compared with no treatment. The high recurrence rates after resection have led numerous investigators to evaluate preresection and postresection chemotherapy in the hope of decreasing recurrence rates. Only

recently have clinical trials begun to provide evidence of enhanced survival for multimodality therapy involving resection with added chemotherapy or ^{131}I lipiodol. The introduction of ^{90}Y microspheres (Theraspheres) appears to offer the promise of relatively nontoxic tumoricidal internal radiotherapy to the liver and appears to be a major therapeutic addition to our treatment choices, and its role alone or in combination with other therapies is just beginning to be explored. The advent of multiple clinical trials for new agents that inhibit either the cell cycle or angiogenesis or both (new chapter) has diminished enthusiasm for chemotherapy, since these agents appear to be less toxic and may enhance survival, even for advanced disease. Some of these agents are taken orally, which makes them even more attractive. In addition, we are beginning to enter the phase of genomics (new chapter) and proteomics (new chapter) as applied to many tumor types, including HCC. This raises the possibility of being able to categorize patients into prognostic subsets, prior to any therapy. We are just at the beginning of the age of cell cycle modulating factors including hormones, growth factors, and growth factor receptor antagonists and agents that specifically alter defined aspects of the cell cycle. Since the mechanisms of many of these agents are known, we are entering the era of personalized medicine and the rational selection of suitable treatment drugs for an individual patient. For all these reasons, it seemed reasonable to us to produce a book that presents much of current therapy and current thinking on HCC. This is an exciting time to be in the field of HCC basic science as well as clinical management, as so many changes are simultaneously occurring at multiple levels of our understanding and management of the disease, and suddenly there are many new choices of therapy to offer our patients. All the original chapters have also been updated and enhanced.

Philadelphia, PA
March 2009

Brian I. Carr

Preface to the First Edition

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nor are you free to desist from trying.

—Talmud, Avot

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The increasing numbers of chronic hepatitis C virus carriers in the United States and subsequent increased incidence of HCC seen in most large medical centers means that it is no longer an uncommon disease for most gastroenterologists or oncologists to encounter.

During the times when liver resection or systemic chemotherapy were the only real therapeutic modalities available, the outcomes were generally dismal, especially because most patients presented with advanced-stage tumors. Several recent factors seem to have changed this. They include the more frequent use of aggressive surveillance by ultrasound and computed tomography (CT) scanning in patients who have chronic hepatitis or cirrhosis from any cause (and thus are known to be at risk for subsequent development of HCC) to detect tumors at an earlier and therefore more treatable stage. Advances in CT scanning, particularly the introduction of multihead fast helical scans, mean that this vascular tumor can often be detected at an earlier stage, or multiple lesions can be diagnosed when only large single lesions were formerly seen, so that unnecessary resections are not performed.

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Liver transplantation has had a profound effect on the therapeutic landscape. There have always been two hopes for this modality: namely, to eliminate cirrhosis as a limiting factor for surgical resection and also to extend the ability of the surgeon to remove ever-larger tumors confined to the liver. Regional chemotherapy and hepatic artery chemoembolization have been around for a long time and have been practiced mainly in the Far East and Europe.

There has not been a consensus for which drug or drug combination is best or whether embolization is important and, if so, what type and size of particle are optimal. Although there is still no consensus on these matters, it has recently become clear from two randomized controlled clinical trials that hepatic artery chemoembolization for unresectable nonmetastatic HCC seems to bestow a survival advantage compared to no treatment. The high recurrence rates after resection have led numerous investigators to evaluate preresection and postresection chemotherapy in the hope of decreasing recurrence rates. Only recently have clinical trials begun to provide evidence of enhanced survival for multimodality therapy involving resection and either chemotherapy or ¹³¹I-lipiodol. The introduction of ⁹⁰Yttrium microspheres, which

appear to offer the promise of relatively nontoxic tumoricidal therapy to the liver, appears to be a major therapeutic addition to our treatment choices, and its role alone or in combination with other therapies is just beginning to be explored.

In addition, we are beginning to enter the phase in which proteomics is applied to many tumor types, including HCC. This raises the possibility of being able to categorize patients into prognostic subsets, prior to any therapy. We are also just at the beginning of the age of cell cycle modulating factors including hormones, growth factors, and growth factor receptor antagonists and agents that specifically alter defined aspects of the cell cycle.

For these reasons, it seemed reasonable to produce a book that represents much of the current therapy and thinking on HCC. Admittedly, there is a bias toward expressing the experience of one center, the Liver Cancer Center at the University of Pittsburgh Starzl Transplant Institute, in which over 250 new cases of HCC have been seen each year for the last 15 years. This is an exciting time to be in the field of HCC basic science as well as clinical management because so many changes are simultaneously occurring at multiple levels of our understanding and management of the disease.

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Hepatocellular Carcinoma

Diagnosis and Treatment

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