Hepatocellular Carcinoma: Fighting the Rising Tide

This issue of *Cancer Control* reviews the various issues involved in the treatment of hepatocellular carcinoma (HCC) and discusses recent developments in surgery, interventional radiology, radiation therapy, and chemotherapy.

While HCC has a low profile within North America, it has the most rapid increase in death rate among the three cancers, with increasing mortality over the last 15 years (the other two are melanoma and esophageal cancer). The incidence of HCC varies around the world. The age-standardized incidence rates of HCC per 100,000 in southeastern Asia in 2002 were 18.3 among males and 5.7 among females, with corresponding mortality rates of 17.2 and 5.4. In contrast, the incidence rates for males and females in North America were 5.3 and 2.0, with corresponding mortality rates of 4.4 and 1.9. These rates in the United States have been slowly rising. The hepatocellular death rate among males increased 47% between 1990 and 2005, from 5.27 to 7.6 per 100,000, and among females it increased 27%, from 2.51 to 3.9 per 100,000. Overall, HCC is the sixth most common cause of cancer death in the United States among males and the eighth most common among females. However, perhaps because historically there have been few treatment options, it has not been a high-profile cancer.

Overwhelmingly, the common etiologic factor for the development of HCC is hepatitis B (HBV) and C (HCV) infection combined with cirrhosis. The annual risk of developing HCC among noncirrhotic, HBV-infected Southeast Asians is 0.5%. The risk of among noncirrhotic, HBV-infected Caucasians is much lower, below 0.2%. However, the risk among all cirrhotic HBV-infected patients rises to approximately 2% per year. In low HBV/HCV areas, such as North America and Europe, alcoholic cirrhosis is a strong risk factor for the development of HCC. A Swedish case-control study found a 22-fold increase in HCC risk among patients with alcoholic cirrhosis. The same study found a 130-fold increase among patients with chronic viral hepatitis and cirrhosis and a 170-fold increase in patients with all three conditions. Other factors known to increase the risk of HCC are aflatoxin exposure and cigarette smoking. Suspected agents associated with HCC include obesity, diabetes, the use of oral contraceptives, and iron overload.

Ideally, early detection would allow the discovery of treatable, curable cancers. However, the low risk of HCC among noncirrhotic HBV or HCV Western patients reduces the cost-effectiveness of screening for HCC in this population. Screening may be cost-effective among infected and noninfected cirrhotic patients who are eligible for potentially curable treatment. Formal criteria are available for determining who may benefit from aggressive treatment. For effective screening, patients need to be able to tolerate an aggressive surgery, whether resection or liver transplantation. These are patients with a MELD (Model for End-stage Liver Disease) score < 10 or Child-Pugh class 1. Bruix et al have suggested a screening paradigm. Patients are screened with an alpha-fetoprotein (AFP) and ultrasound of the liver every 6 months. If there is no nodule and the AFP is normal, then surveillance can continue. If there is no nodule and the AFP is elevated, then a spiral CT should be obtained. If that is negative, then screening is resumed. If a nodule on ultrasound is < 1 cm, the study should be repeated every 3 months until the nodule resolves or grows to > 1 cm. If a nodule on ultrasound is > 1 cm and < 2 cm, then a fine needle aspiration biopsy should be obtained. If the nodule is > 2 cm, a biopsy can be obtained, but if a second study such as angiography, MRI, or CT is consistent with an HCC (ie, showing arterial hypervascularization) or if the AFP is > 400, a clinical diagnosis of HCC can be made. Utilizing these criteria, approximately half of screened patients will have solitary nodules suitable for potentially curable treatment. The fact that many of these patients never have biopsies is unique among cancers. This contributes to the slow progress in improving treatment, because the genetic signature that is important in other cancers can never be studied.

Once a patient is diagnosed with HCC, the disease needs to be staged. Dr Outwater discusses the radiological evaluation of this cancer. HCC is generally negative on positron-emission tomography (PET), and PET positivity is a negative prognostic factor. CT scans of the chest and abdomen can identify metastases. A three-phase CT or MRI can identify other disease within the liver. An angiogram, with possible transarterial chemoembolization at the same time, can also identify other intrahepatic lesions.

After staging is completed, treatment options can be discussed. Because of the variety of treatments available, it is important that all HCC cases be discussed in a multidisciplinary tumor board and that the treating facility has all of the potential treatment options available.

The most aggressive curative treatment is liver transplantation. As discussed in the article by Dr Alsina...
and coworkers, the accepted criteria for eligibility for transplantation, as defined by the Milan criteria, are single tumors $\leq 5$ cm, or 3 nodules $\leq 3$ cm each, without macrovascular invasion and with no metastatic disease. A newer approach is to try to downstage the cancer to meet these criteria and then wait to see if the patient progresses before transplantation. This may expand the curative role of transplantation. However, long-term follow-up is still needed. The role of adjuvant therapy after transplantation still needs to be explored.

Until recently, the only treatment for localized, inoperable HCC was embolization, and it is still the standard of care. The liver is unique in that the main vascular supply of the normal parenchyma is the venous system and that of the tumor is the arterial system. This allows selective destruction of the tumor vascular system. Dr Davis’s article focuses on the different forms of embolization. Currently most tumors are treated with chemoembolization. A newer technique discussed is $^{90}$Y radioactive treatment. Although the treatment involves radioactive microspheres injected by arterial catheterization, the primary mode is from the radiation and not embolization. This technique is still in its infancy and should be performed within a controlled environment.

In the next article in this issue, Dr Hoffe and colleagues describe another new technique for localized treatment, highly conformal radiotherapy. Until recently the liver was considered too sensitive for radiation to be an effective treatment. However, modern methods allow the delivery of high doses of x-rays to the tumor with relative sparing of the normal parenchyma. As with all new techniques, the therapy must be used with caution because potential acute and late toxicities are not well sufficiently known. Dr Sawrie and coworkers outline the normal toxicity guidelines used in several large trials of liver irradiation for hepatocellular cancer or liver metastases. The underlying data are sparse and need confirmatory data. Most importantly, the risk of damage and the lack of detailed toxicity knowledge emphasize that this approach must be considered experimental and should be done at advanced centers in prospective trials.

Finally, little progress can be made in the curative treatment of HCC until active systemic treatments are available. Sorafenib, a tyrosine kinase inhibitor, is the first systemic treatment approved for use in metastatic HCC. A randomized trial showed an increase in median survival from 7.9 months to 10.7 months.7 Current studies are bringing sorafenib into the adjuvant setting. Other systemic agents, including potential immunological agents, are also being investigated.

It is promising that as the incidence of HCC rises, new treatment options are being developed. The combination of aggressive local treatments with active systemic agents should lead to increasing survival and cure rates and will possibly remove HCC from the list of cancers that portend increasing annual mortality.

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