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Evolving Strategies in Hepatocellular Carcinoma Screening and Treatment: A Discussion Post-AASLD 2008

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Abstract

Hepatocellular carcinoma is the fifth most common form of cancer worldwide. The implementation of screening and surveillance greatly increases the chance of detecting hepatocellular carcinoma at an early and highly treatable stage. Current guidelines recommend serum alpha fetoprotein measurements and ultrasound every 6 to 12 months for the screening and surveillance of high-risk patients. Once hepatocellular carcinoma is suspected, diagnosis is confirmed using magnetic resonance imaging or computed tomography; a liver biopsy may also be necessary. The application of staging and prognosis systems, such as the Barcelona Clinic Liver Cancer algorithm, provide essential guidance when evaluating the optimal treatment strategy to present to patients. Depending upon the stage of disease, resection, transplant, transarterial chemoembolization, ablative therapies, or the targeted oral agent sorafenib may be recommended. While patients with advanced disease have little chance of cure, novel tyrosine kinase inhibitors (TKIs) and other emerging therapies are aimed at significantly prolonging patient survival.

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with hepatocellular carcinoma.

Statement of Need/Program Overview: The incidence rate of hepatocellular carcinoma (HCC) is the fifth highest among tumors worldwide and similar in size to the death rate. Hepatic cirrhosis has been recognized as the most important risk factor for the development of HCC. Treatment options for HCC continue to expand and improve. Techniques for radiofrequency ablation and transarterial chemoembolization have allowed for more successful treatment in the early stages of disease. For patients with later-stage disease, improvements in terms of survival time and time-to-tumor progression have been shown with the use of the oral targeted therapy sorafenib. Future research will investigate the use of all of these modalities in different combinations and at different timepoints to further optimize their efficacy.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe the importance of new study findings from recent abstracts, posters and clinical presentations in the natural history of HCC-including those delivered at AASLD 2008.
2. Outline the clinical implications of the results of pivotal clinical trials that have potential to impact the use of novel multikinase-targeting therapies in evaluating optimal medical treatment regimens and the effect on extending survival in HCC.
3. Describe how to integrate the latest knowledge and methods for treating patients with HCC into clinical practice in an effort to improve current prognosis statistics.
4. Identify future research directions for all therapies in HCC in light of recent clinical data.

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Strategies for Early Detection of HCC

Hashem B. El-Serag, MD, MPH

Hepatocellular carcinoma (HCC) is a highly fatal cancer that affects approximately half a million people worldwide every year.[1] At a population level, the median survival with HCC is between seven to eight months and the five-year survival is less than 10%.[2,3] In the United States, HCC has traditionally been regarded as a rare cancer. However, over the past 15 years, the incidence of HCC has more than doubled, largely due to hepatitis C virus (HCV) infection that was acquired 20 to 30 years earlier.[4] Unfortunately, there have been few improvements in survival rates over the past decade, thus highlighting the importance of detecting HCC at an early stage when potentially curative therapies can be applied.

Recently, the rationale for HCC screening has been more greatly recognized for a number of reasons, the first of which is the availability of potentially curative therapy such as liver transplant and local ablation therapy. These therapies were not widely available, tested, or recognized just a decade ago. Second, the publication of a randomized controlled trial by Zhang and associates[5] that demonstrated the efficacy of screening in reducing cancer-related death provided a major boost to HCC screening. In this study of nearly 19,000 hepatitis B virus (HBV)–infected patients in China, screening with alpha fetoprotein (AFP) and abdominal ultrasound performed every six months resulted in a 37% reduction in HCC-related mortality.[5] Cancers detected as a result of a screening or surveillance program tend to be smaller in size, diagnosed at an earlier stage, and subjected to potentially curative therapy more often than cancer detected in patients who present with symptomatic tumors outside of a screening or surveillance program.[6-9] As a result of this study and others, the recommended surveillance interval for at-risk patients is every six months, although periods of up to 12 months have also been recommended and may be equally effective.[6,7,9]

Identifying Candidates for Screening and Surveillance

The primary risk factor for HCC is the presence of liver cirrhosis. In the presence of liver cirrhosis, the annual incidence of HCC ranges between 2 to 5%.[10-12] Therefore, over a course of ten years, the cumulative incidence of HCC in a cirrhotic patient may reach as high as 50%. Cumulative evidence from randomized, controlled trials and observational studies has led the American Association for the Study of Liver Diseases (AASLD) to include all patients with cirrhosis in their recommendations for screening and surveillance for HCC.[9] The most common causes of cirrhosis in the United States are HCV, alcoholic liver disease, and HBV. The AASLD further recommends the surveillance of patients infected with HBV, even in the absence of cirrhosis, if the patient is a man older than age 40, a woman older than age 50, or if there is a family history of HCC. The disease state, family history, ethnicity, and age are also factored in the high-risk groups for whom applications of surveillance are recommended (Table 1).[3,9]

Application of Serum Markers and Biomarkers

The currently recommend tools for HCC screening are a combination of AFP and ultrasound at a frequency of every 6 to 12 months.[6,7,9] The use of serum AFP as a single screening test is strongly discouraged. The AASLD currently recommends a cut off of 20 ng/ml AFP as an upper limit.[9] This cut off has low sensitivity ranging from 25% to 65% for detecting HCC. Patients with chronic liver disease —especially those with a high degree of hepatocyte regeneration, as observed in HCV infected patients—can express elevated serum AFP in the absence of malignancy. This contributes

Table 1. Screening for Hepatocellular Carcinoma

Non-hepatitis B cirrhosis
- Hepatitis C
- Alcoholic cirrhosis
- Genetic hemochromatosis
- Primary biliary cirrhosis
- Possibly: Alpha1-antitrypsin deficiency, non-alcoholic steatohepatitis, autoimmune hepatitis

Hepatitis B carriers
- Asian males >40 years
- Asian females >50 years
- All cirrhotic hepatitis B carriers
- Family history of HCC
- Africans over age 20

Data from Bruix and Sherman.[9]

to the low accuracy of this test. Therefore, AFP is considered inadequate as a sole screening test and must be used in combination, if at all, with ultrasound.

In countries such as Japan, other serum markers have been developed and are used more frequently. These markers include lectin-bound AFP, which is the moiety that is more specific for HCC, and des-gamma carboxy prothrombin (DCP). Although both of these markers have been studied and used, information from the available studies indicate that they do not provide significant improvements in sensitivity and specificity over AFP alone.[13,14] Therefore, imaging is still considered the cornerstone of HCC screening.

Application of Imaging Techniques

The effectiveness of an ultrasound-screening test partly depends upon the experience of the examiner. In addition, it is less sensitive in obese patients and less accurate in the presence of a nodular liver or a small tumor. Despite these difficulties, recent studies indicate a sensitivity that is greater than 60% and specificity greater than 90% for the use of ultrasound as an HCC surveillance test. Although computed tomography (CT) scans and magnetic resonance imaging (MRI) are also used, there are limited data from large studies that support their efficacy in HCC screening (as distinct from diagnosis or case finding).

If the results from AFP measurements or ultrasound readings suggest that a patient may have HCC, imaging is the gold standard for the diagnosis and staging of the tumor. The most reliable diagnostic tests are triple phase CT scanning or contrast-enhanced MRI. Hepatic angiography has generally fallen out of favor in most practice settings. CT and MRI are useful in the diagnosis of HCC due to their ability to detect changes in blood supply to the liver. Blood supply to HCC is derived predominantly from the hepatic artery, whereas the remainder of the liver receives both arterial and portal blood. The hallmark of HCC during CT or MRI is the presence of arterial enhancement followed by delayed hypo-density of the tumor in the portal venous and delayed phases. This phenomenon is known as washout of contrast. The presence of arterial enhancement followed by washout has a sensitivity and specificity of greater than 90%. Several studies have compared the diagnostic accuracy of MRI versus CT scans.[15-17] These studies have shown that MRI is slightly more accurate in the characterization and diagnosis of HCC. Neither MRI nor CT scans performed well when diagnosing smaller tumors. However, MRI performed marginally better in this scenario.

The diagnosis of HCC has witnessed a major change with the development of accurate noninvasive imaging but accurate diagnosis also incorporates histology in some instances (Figure 1). Diagnosis of HCC can be confidently established in a patient with cirrhosis for a mass of at least two centimeters in size with MRI or CT scans that shows characteristic enhancement followed by washout. However, a focal hepatic mass in which there is an atypical imaging finding either in the absence of arterial enhancement and/or washout necessitates a liver biopsy. Nodules that are between one to two centimeters require two imaging modalities, as opposed to larger nodules in which one imaging modality is sufficient. Nodules that are smaller than one centimeter are difficult to image accurately and are too small to sample with a biopsy; these nodules should be followed by repeated imaging every three to six months. If further growth has not been observed over the period of two years, then routine surveillance every six months is suggested.

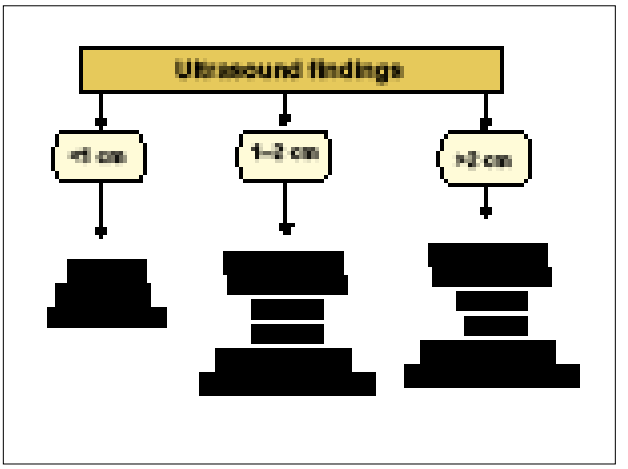

Figure 1. Guidelines for diagnosis of hepatocellular carcinoma (HCC) in a patient with cirrhosis undergoing HCC surveillance.

Typical features of HCC=vascular nodule on arterial phase with washout in delayed phases; CT=computed tomography; MRI=magnetic resonance imaging; US=ultrasound.

Adapted from Bruix and Sherman.[9]

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Current Therapeutic Options for HCC

Robert G. Gish, MD

Selecting Patients for Resection or Transplant

Nearly 20,000 cases of primary liver cancer are diagnosed in the United States each year, with the number of worldwide cases exceeding 500,000.[1,2] Transplant provides the best option for a cure in the largest number of patients. However, a liver transplant is not a viable option for many of these people due to the shortage of organs and the resource-intense nature of the process. Liver resection offers an alternative option for treating HCC. Unfortunately, the risk of resection often outweighs the benefit of a cure for patients with cirrhosis and portal hypertension or synthetic dysfunction. These patients are at an increased risk for extensive bleeding, liver decompensation, or even death. Thus, it is very important to understand the staging systems for selecting those patients that are candidates for transplantation versus resection.

Staging systems provide guidance when evaluating prognosis and therapeutic interventions. Dr. Marrero and colleagues conducted a comparative study of 7 different staging systems to determine which was best able to predict the survival of a cohort of HCC patients in the United States.[3] This study found that the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy,[4] which includes aspects of treatment, performance status, tumor burden, and liver function, was best able to predict patient survival.[3]

The BCLC algorithm is very useful when evaluating what therapeutic options to present to a patient (Figure 2). In Stage 0, the patient has excellent performance status and a Childs-Pugh score A, evidenced by normal synthetic function and minimal portal hypertension. The tumors are small (≤2 cm) with a single lesion. If bilirubin is normal (1.2 mg/dL) in these patients, then resection is recommended. Patients characterized by elevated portal pressure but small tumors (a single lesion up to 5 cm or ≤3 lesions of 3 cm or smaller) fit what is called the Milan criteria, which was originally published by Mazzaferro and colleagues in the *New England Journal of Medicine*.[5] Patients who meet this criteria and receive a transplant have a very high long-term cancer-free, tumor-free survival that exceeds 85% at 4 years.[5] Therefore, patients in the United States who meet the Milan criteria receive extra points for organ allocation under the Model for End-Stage Liver Disease (MELD), resulting in an 80% chance of transplantation within 3 to 9 months.

Radiofrequency Ablation

Stage A patients with no more than three nodules of 3 cm or smaller are candidates for liver transplant, but only in the absence of associated diseases. In the presence of comorbid conditions such as advanced age, diabetes, peripheral vascular disease, or cardiopulmonary disease, ablative techniques are recommended. There are a variety of ablative techniques that can be offered to patients.[6] Percutaneous ethanol injection (PEI) is the least expensive and is primarily used in developing countries. Radiofrequency ablation (RFA) is commonly used in the United States, Europe, and Asia due to the availability of radiologists and surgeons skilled in this therapeutic modality. In 2003, Lencioni and colleagues conducted a study comparing the efficacy of PEI versus RFA in HCC patients with cirrhosis.[7] The patients were characterized by low bilirubin levels (1.5 mg/dL) and a single lesion of 5 cm or less or up to three lesions that were of 3 cm or smaller. This study found that patients treated with RFA had superior 2-year local recurrence-free survival rates compared with PEI (96% vs 62%). In addition, RFA may provide a viable alterative to resection. In a prospective randomized trial comparing RFA to resection, Chen and coworkers found that patients with a single HCC lesion of 5 cm or smaller and normal bilirubin levels (1.2–2.2 mg/dL) exhibited comparable disease-free survival rates for the 4 years of the study following either treatment modality.[8] This study demonstrates that RFA is comparable with resection and provides a less invasive option for small tumors. Although it is rare that patients will achieve a cure with ablation, RFA can significantly improve short and intermediate term survival.

Transarterial Chemoembolization

Patients with more advanced disease who are not candidates for resection, transplant, or ablation should receive treatment with transarterial chemoembolization (TACE) or other

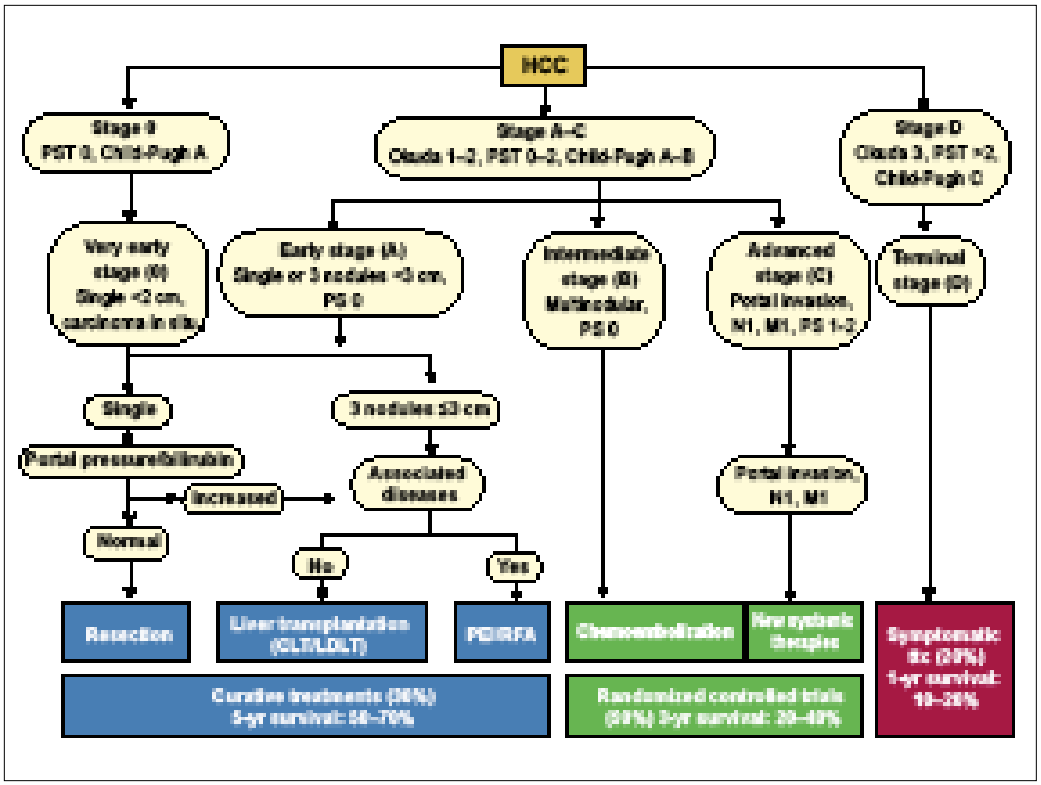

Figure 2. Barcelona Clinic Liver Cancer algorithm for staging and treatment of hepatocellular carcinoma (HCC).

CLT=cadaveric liver transplant; LDLT= living donor liver transplant; PEI=percutaneous ethanol injection; PS=performance score; RFA=radiofrequency ablation.

Adapted from Llovet et al.[4]

embolic processes as a means to slow tumor progression.[9,10] TACE is typically offered to patients with intermediate stage tumors (Stage B). These patients are characterized by multinodular disease with a good performance status, some synthetic dysfunction, and a Childs-Pugh score B, although a Childs-Pugh score A may also be included. In TACE, an extraintestinal catheter is placed, typically in the groin, and then fed into the hepatic artery through the abdominal aorta. Angiographic localization of the tumor is followed by the injection of a high-viscosity mixture of iodinated soybean oil that is mixed with up to three forms of chemotherapy (adriamycin, mitomycin, and/or cisplatin). The iodinated soybean oil collects in the highly vascular region of the tumor. The slow washout or reabsorption rate of the oil keeps the chemotherapy localized. The embolic process, utilizing gelfoam, occludes the feeding arterial branch that goes into the tumor, thus blocking blood flow to the tumor. The efficacy of this approach was demonstrated in a randomized, controlled study of patients with unresectable HCC published by Llovet and colleagues in 2002.[11] At 1 and 2 years, the survival probabilities were 82% and 63% for chemoembolization versus 63% and 27% for conventional therapies (*P*=.009). The improved short-term and intermediate-term survival rates with TACE have led to its use as a bridge therapy to liver transplant or resection. It has been suggested that TACE will increase the chance of a patient staying on the transplant list and acquiring an organ, as well as decrease recurrence and prolong survival.[12-16] However, the efficacy of TACE as a bridge therapy requires confirmation with further studies.

TACE may also be effective when used as combination therapy with RFA for larger tumors. In a recent study by Cheng and colleagues[17] patients with HCC lesions larger than 3 cm were randomized to receive TACE alone, RFA alone, or TACE followed by RFA. Patients receiving the combination of TACE plus RFA had significantly improved overall survival compared with TACE or RFA alone (median survival: 37 months, 24 months, and 22 months, respectively).

Embolization can also be performed with doxorubicin-coated (DC) beads or yttrium microspheres. DC beads can be delivered to the tumor by transarterial embolization. The beads slowly release doxorubicin directly into the tumor, thus limiting the potent systemic effects of doxorubicin while simultaneously providing an ischemic embolic effect that can cut off blood flow.[18,19] DC beads would be most beneficial for patients who are at risk of decompensation with standard TACE or standard chemoembolization. Because DC beads are focal, the risk for decompensation is reduced. Results from a phase I/II trial confirm that DC beads are a safe and effective option for treating HCC.[19] Yttrium microspheres are resin or glass

spheres labeled with radioactive yttrium-90 that are also delivered directly to the tumor site.[20,21] Once the radiation dissipates, the patient can go for surgical resection or transplantation.[22] Yttrium microspheres can be recommended for patients with good liver function but a large tumor with possible vascular invasion. Initial studies suggest that treatment with yttrium microspheres may improve survival and reduce risks of major complications.[21,23]

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Medical Options for Late-Stage Tumors and Ongoing Research for Future HCC Treatment

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Sorafenib

The most important aspect of successful HCC treatment is accurate staging. Patients at BCLC stage C are characterized by multi-nodular tumors, a Childs-Pugh score A or B, the presence of portal vein involvement, and possibly extrahepatic metastasis. Currently, the best treatment option for these patients is sorafenib, a RAF kinase receptor tyrosine kinase inhibitor (TKI) with both antiproliferative and antiangiogenic activity.[1] An international, open-label phase II trial of sorafenib was conducted in 137 patients with inoperable HCC and a Childs-Pugh score of A or B.[2] Patients received oral sorafenib 400 mg BID in 4-week cycles. The primary endpoints included overall tumor response (according to modified WHO criteria) and safety assessments. The study found that 46/137 patients (33%) had stable disease for at least 16 weeks when treated with sorafenib, with partial or minor response observed in 11 patients. The most common adverse events were diarrhea (43.1%), hand-foot skin reaction (30.7%), and fatigue (29.9%). Median time to progression in this study was 5.5 months.

Based upon the promising results of the phase II study, a multicenter, double-blind, placebo-controlled phase III study was recently completed. The Sorafenib HCC Assessment Randomized Protocol (SHARP) study[3] was conducted in 602 patients with advanced HCC and Childs-Pugh A disease, who had not received previous systemic treatment. Macroscopic vascular invasion (38%) and extrahepatic spread (51%) were noted at baseline. Patients were randomized to receive either sorafenib 400 mg BID (n=299) or placebo (n=303). The primary endpoint was overall survival (OS) and time to symptomatic progression. The patients in the sorafenib group had a median OS of 10.7 months versus 7.9 months in the placebo group (hazard ratio: 0.69; 95% CI: 0.55–0.87; $P<.001$). There was no significant difference in the median time to symptomatic progression among the groups. However, there was a significant difference in the median time to radiographic progression (5.5 months in the sorafenib group versus 2.8 months in the placebo group; hazard ratio for progression in the sorafenib group, 0.58; 95% CI: 0.45–0.74; $P<.0001$). Overall, 80% of patients developed some type of adverse event, but the most common were diarrhea (39%), fatigue (22%), hand-foot skin reaction (21%), rash (16%), alopecia (14%), and anorexia (14%). These adverse events can improve with dose reduction or halting the medication. Importantly, there was no significant difference in the percentage of patients with liver dysfunction or bleeding. Overall, this large phase III study found that sorafenib prolonged survival and radiographic progression compared to placebo and should be the first-line treatment for advanced HCC.

A similar phase III study was conducted in Asian/Pacific patients with advanced HCC and Childs-Pugh score A.[4] Microvascular involvement was observed in 36% of patients and evidence of extrahepatic spread was observed in 69% of the patients. Overall, the patients in this study had more advanced disease than the patients in the SHARP study, with 96% falling within BCLC stage C. Patients were randomized to receive sorafenib 400 mg BID (n=150) or placebo (n=76). The endpoints were OS, time to progression, time to symptomatic progression, and safety. The median OS in the sorafenib group was 6.2 months compared to 4.1 months in the placebo group (hazard ratio 0.67; 95% CI: 0.49–0.93). The median time to progression was 2.8 months in the sorafenib group versus 1.4 months in the placebo group (hazard ratio 0.58; 95% CI: 0.42–0.80). There was no significant difference between the two groups in the time to symptomatic progression. Stable disease was observed in 54% of the sorafenib group versus 28% of the placebo group. Major adverse events included hand-foot skin reaction (45%), diarrhea (26%), alopecia (25%), fatigue (20%), rash (20%), hypertension (19%), and anorexia (13%). Sorafenib improved the overall survival of Asian/Pacific patients with advanced HCC, although the median survival was less than was observed in the SHARP study. Both the SHARP and the Asian-Pacific study have demonstrated that sorafenib improved OS in patients with advanced HCC, further supporting the use of this drug as the first-line treatment for these patients. Future studies of new agents for advanced HCC should be compared against sorafenib.

Other TKI Agents Under Investigation

Sunitinib is a TKI that has activity against vascular endothelial growth factor receptors (VEGF-R) and platelet-derived growth factor receptors (PDGF-R). A recent phase

II study was conducted by Zhu and colleagues to evaluate the efficacy and safety of sunitinib for the treatment of unresectable or metastatic HCC.[5] Thirty-four patients received oral sunitinib 37.5 mg daily for 4 weeks every 6 weeks. The median OS was 9.9 months (95% CI: 7.5–11.7) and 16 patients had stable disease for at least 12 weeks. Reported toxicities included elevated ALT (18%), lymphopenia (15%), neutropenia (12%), thrombocytopenia (12%), and fatigue (12%). Hyperbilirubinemia and hypertension were reported in 6% of patients. In a similar study by Faivre and colleagues, 37 European and Asian patients with unresectable HCC were treated with sunitinib at 50 mg daily for 4 weeks every 6 weeks.[6] Stable disease was observed in 13/37 (35%) patients at 3 months and 8/37 (21.6%) patients at 6 months. The median OS was 45 weeks and the median time to tumor progression was 21 weeks. Grade 3 or greater adverse events included thrombocytopenia (35%), neutropenia (24.3%), central nervous system symptoms (24%), asthenia (22%), and hemorrhage (14%). These two clinical studies suggest that sunitinib may have some activity against HCC, but the reported toxicities and adverse events are cause for concern with regard to moving forward with phase III trials.

The other agent that has been recently studied is erlotinib. Erlotinib is an epidermal growth factor receptor (EGF-R) TKI. As EGF-R plays a significant role in the cascade of RAF kinase activation, drugs targeting this receptor will result in anti-angiogenesis and antiproliferative effects. In 2005, Phillip and associates published the results of a phase II study of erlotinib in 38 patients with unresectable or metastatic HCC.[7] The median OS was 13 months. Disease control was observed in 59% of patients with 12/38 patients progression-free at 6 months. Adverse events included skin rash (13%) and diarrhea (8%). Erlotinib has also been used in combination with bevacizumab, a VEGF monoclonal antibody.[8] This study included 40 patients with advanced HCC, a Childs-Pugh score A or B, and performance status 0, 1, or 2. Patients received bevacizumab 10 mg/kg every 14 days and oral erlotinib 150 mg daily for 28-day cycles. The primary endpoint of 16-week progression-free survival was reached by 62.5% of patients. The median OS was 68 weeks. However, hypertension was observed in 6/40 patients (15%) and gastrointestinal bleeding occurred in 5/40 patients (12.5%). This initial study suggests that bevacizumab and erlotinib may not be a safe drug combination. Further safety studies of these agents should be conducted before progressing to a phase III trial.

Other TKIs are currently in development. Brivanid alaninate is an oral inhibitor of VEGF-R and fibroblast growth factor receptor (FGF-R) tyrosine kinase. Data are limited on its use in HCC, but results from a phase I trial of patients with advanced or metastatic cancer are promising.[9] The PI3K/AKT/mTOR pathway is also gaining interest as a therapeutic target in HCC. The use of a TKI such as sorafenib, sunitinib, or erlotinib in combination with a drug targeting the AKT pathway may be particularly effective in treating HCC. Currently, there are no clinical trials targeting the PI3K/AKT/mTOR pathway, but this will likely change over the next year.

References

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2. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol.* Sep 10 2006;24(26): 4293-4300.
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8. Thomas MB, Morris JS, Chadha R, et al. Phase II Trial of the Combination of Bevacizumab and Erlotinib in Patients Who Have Advanced Hepatocellular Carcinoma. *J Clin Oncol.* Jan 12 2009.
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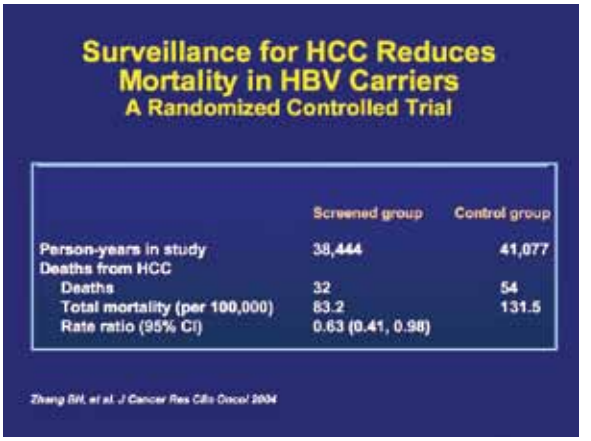
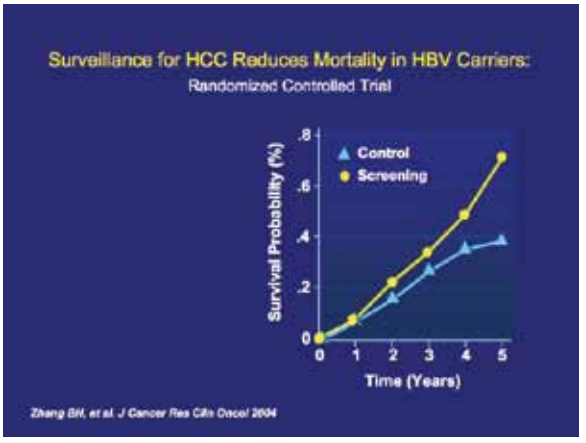
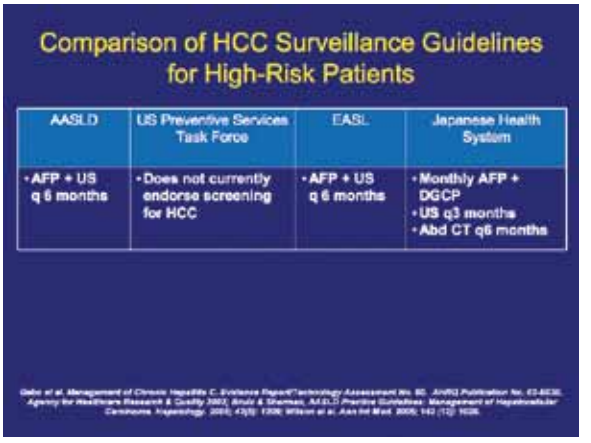
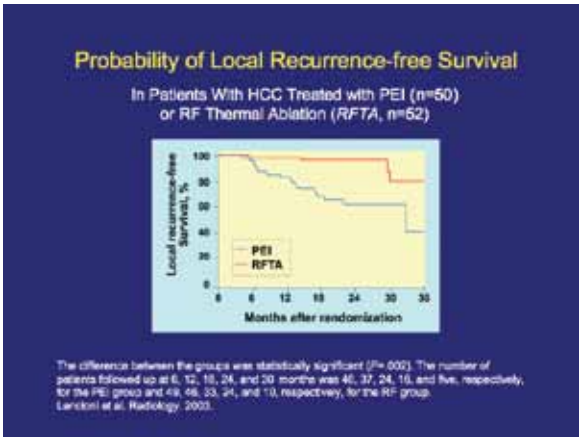
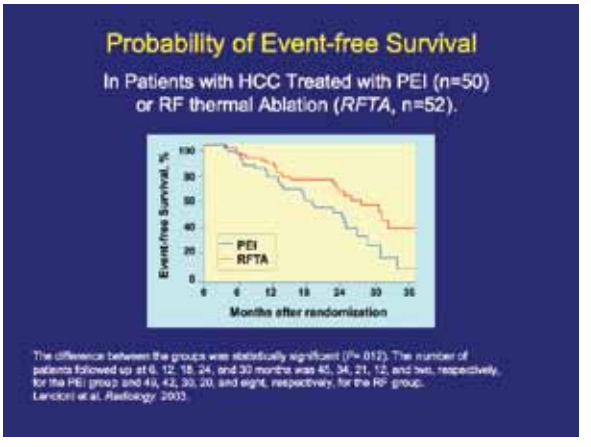








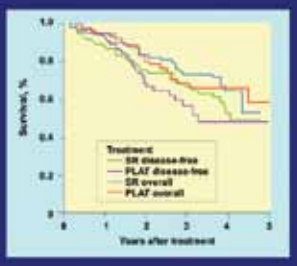


Overall and Disease-free Survivals

For Patients Randomized to Percutaneous Local Ablative Therapy (PLAT)

n=60, including 19 patients who withdrew their consent after randomization and received surgical resection (SR)

Chen et al, Ann Surg. 2006.



Milan Criteria Liver Transplantation

- 1 nodule 2.0 to 5.0 cm
- 2 to 3 nodules all ≤3.0 cm
- No gross intrahepatic portal or hepatic vein involvement on imaging
- No lymph node or distant metastasis or extrahepatic portal or hepatic vein involvement

Mazzaferro V, et al. *N Engl J Med.* 1996.

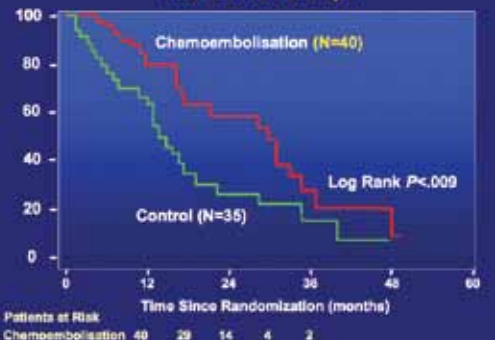
Early versus Late Recurrence after Liver Resection for HCC

- Following surgery for HCC, 213 patients were evaluated for risk factors related to the risk of recurrence
- Intrahepatic recurrence was observed in 143 patients
  - 109 early (<2 years) and 34 late recurrences (>2 years)
  - Independently prognostic factors for risk of recurrence were
    - Cirrhosis
    - Chronic active hepatitis (CAH)
    - HCV positivity
  - Cumulative effect for multiple risk factors (92.5% of recurrences in patients with all 3 factors)
  - For early recurrences, neoplastic vascular infiltration plus cirrhosis, HCV positivity, CAH, and transaminases were significant
  - Only cirrhosis was related to late recurrence
  - Survival rate was significantly better in late than in early recurrence
    - After radical treatment, survival was comparable with the group of patients without recurrence

Authors' Conclusions: Early and late recurrences are linked to different predictive factors. The modality of presentation of the recurrence together with the feasibility of a radical treatment are the best determinants for the prognosis.

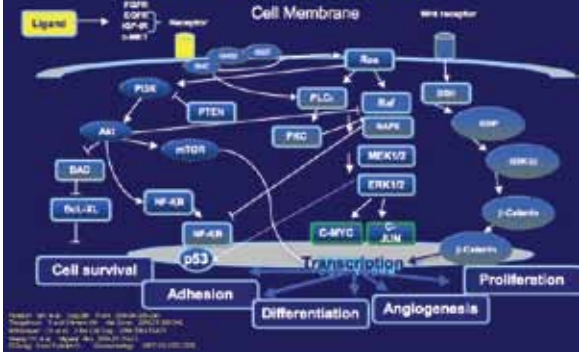
Portolani N, et al. *Ann Surg.* 2006.

Survival Curves of the Chemoembolisation and Control Groups

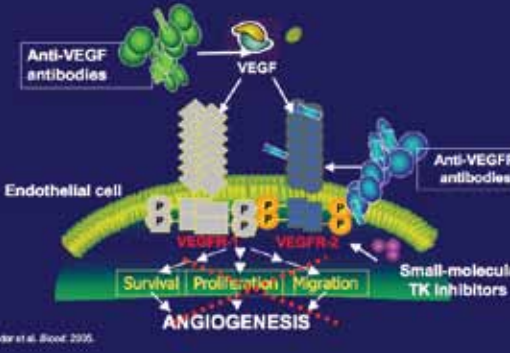


Llovet J, et al. *Lancet.* 2002.

Signaling Pathways for Cell Proliferation and Survival



Agents Targeting the VEGF Pathway



Podar et al. *Blood.* 2005.

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Notes

Evolving Strategies in Hepatocellular Carcinoma Screening and Treatment

CME Post-Test: *Circle the correct answer for each question below.*

1. According to the randomized trial conducted by Zhang and associates, AFP and ultrasound screening every six months resulted in a ____% reduction in HCC-related mortality.

   A. 15%
   B. 23%
   C. 37%
   D. 54%

2. According to Dr. El-Serag, cancers detected because of screening and surveillance are:

   A. smaller in size
   B. diagnosed at an early stage
   C. more often exposed to potentially curative therapy
   D. All of the above

3. TRUE or FALSE? HCV-infected patients with chronic liver disease can express elevated serum AFP even if tumors are not present.

   A. True
   B. False

4. According to the comparative study by Marrero and colleagues, the _____ staging system was best able to predict the survival of US patients with HCC.

   A. BCLC
   B. CLIP
   C. Okuda
   D. TNM

5. The recurrence-free survival rate of patients who meet the Milan criteria and receive a transplant is approximately _____%.

   A. 55%
   B. 65%
   C. 75%
   D. 85%

6. In the study by Lencioni and associates, treatment with RFA resulted in a 2-year recurrence-free survival rate of ____%, while PEI resulted in a 2-year recurrence-free survival rate of _____%.

   A. 62, 96
   B. 96, 62
   C. 73, 41
   D. 41, 73

7. In the study by Cheng and colleagues, _____ resulted in significantly improved OS for patients with tumors ≥3cm.

   A. TACE
   B. RFA
   C. TACE followed by RFA
   D. RFA followed by TACE

8. In the SHARP trial, treatment with sorafenib resulted in an OS of ____ months, compared to an OS of ____ months in the placebo group.

   A. 10.7, 7.9
   B. 7.9, 10.7
   C. 8.8, 11.1
   D. 11.1, 8.8

9. All of the following are tyrosine kinase inhibitors EXCEPT:

   A. Sorafenib
   B. Sunitinib
   C. Erlotinib
   D. Bevacizumab

10. A phase II study conducted by Zhu and colleagues found that treatment with sunitinib resulted in a median OS of _____ months.

    A. 6.2
    B. 9.9
    C. 10.4
    D. 11.3

Evaluation Form: Evolving Strategies in Hepatocellular Carcinoma Screening and Treatment

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating: 1=Strongly Disagree, 2=Disagree, 3=Neutral, 4=Agree, 5=Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the importance of new study findings from recent abstracts, posters and clinical presentations in the natural history of HCC-including those delivered at AASLD 2008. 1 2 3 4 5
2. Outline the clinical implications of the results of pivotal clinical trials that have potential to impact the use of novel multikinase-targeting therapies in evaluating optimal medical treatment regimens and the effect on extending survival in HCC. 1 2 3 4 5
3. Describe how to integrate the latest knowledge and methods for treating patients with HCC into clinical practice in an effort to improve current prognosis statistics. 1 2 3 4 5
4. Identify future research directions for all therapies in HCC in light of recent clinical data. 1 2 3 4 5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1 2 3 4 5
Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Provided new ideas or information I expect to use	1 2 3 4 5
Addressed competencies identified by my specialty	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

_____

Please list any topics you would like to see addressed in future educational activities.

_____

Additional comments about this activity. _____

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