REVIEW

The Changing Landscape of Hepatocellular Carcinoma
Etiology, Genetics, and Therapy

Erik S. Knudsen,*[†] Purva Gopal,* and Amit G. Singal[†‡]

From the Department of Pathology* the Harold C. Simmons Cancer Center,[†] and the Division of Digestive and Liver Diseases,[‡] Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas

Hepatocellular carcinoma (HCC) represents one of the leading causes of cancer death and has proved to be highly refractory to treatment. Extensive analysis of the disease has demonstrated that it arises predominantly in response to high-risk etiological challenges, most notably hepatitis virus. However, with evolving vaccination and the obesity epidemic, progressively more cases are associated with underlying metabolic dysfunction. Pathologically diverse forms of HCC are observed, and recent sequencing analysis has defined common events that target well-known cancer pathways including β-catenin/Axin, TP53, and RB/CDKN2A, as well as frequent aberrations in chromatin remodeling factors. However, there are a myriad of low frequency genetic events that make each HCC case unique. Gene expression profiling approaches have successfully been deployed for prognostic assessment of hepatocellular carcinoma and to detect the earliest stages of disease. Despite more extensive research, systemic treatment for HCC is exceedingly limited, with only a handful of drugs providing benefit. Ongoing clinical trials are attempting to exploit specific biological dependencies of HCC to improve the dismal prognosis. Overall, the future of HCC treatment will rely on an understanding of the interplay between etiological factors, molecular features of disease, and rational therapeutic intervention. (Am J Pathol 2014, 184: 574—583; http://dx.doi.org/10.1016/j.ajpath.2013.10.028)

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, is the third leading cause of cancer-related death worldwide.[1] It is the fifth most common cause of cancer in men (7.9% of all cancers) and the seventh most common cancer in women (6.5% of all cancers).[2] There is considerable geographic variation in HCC incidence, with the majority of cases occurring in developing countries. More than 75% of HCC occurs in Southeast Asia and sub-Saharan Africa, with incidence rates exceeding 20 per 100,000 individuals. Southern European countries have intermediate incidence rates, whereas the lowest incidence rates (<5 per 100,000 individuals) are found in North America, South America, and Northern Europe.[2]

Etiological Factors

Hepatitis B virus (HBV) is the primary etiological factor for HCC worldwide, particularly in high-incidence areas, such as Asia and Africa, where more than 70% of HCC patients have underlying HBV infection.[3] Annual incidence among HBV carriers from Asia exceeds 0.2% starting at age 40; therefore, HCC surveillance is recommended in Asian males older than age 40 and Asian females older than age 50, even in the absence of cirrhosis.[4] Patients from Africa are particularly at high risk, potentially related to a synergistic effect from aflatoxin exposure, and experts recommend HCC surveillance at an earlier age.[5] HBV-infected patients who are exposed to aflatoxin are 60 times more likely to develop HCC compared to those with neither exposure, which is likely related to HBV modulating the extent that aflatoxins can bind to DNA and result in mutations in the TP53 tumor-suppressor gene.[6]

In Europe and the United States, hepatitis C virus (HCV)-associated cirrhosis is the most common etiological factor, accounting for approximately 60% of HCC cases.[7] The risk of HCC is increased 17-fold in HCV-infected patients compared to HCV-negative patients.[8] However, HCC risk among patients with chronic HCV infection is primarily limited to those with cirrhosis, with an annual incidence rate of 2% to 8%.[9,10] Alcoholic cirrhosis is another well-recognized risk factor for HCC, and alcoholic liver disease has been reported to be a contributing factor in nearly one-third of all HCC cases worldwide.[11,12] However, HCC incidence rates among patients with alcoholic cirrhosis may be overestimated, given that several studies linking alcoholic cirrhosis and HCC predated routine testing for HCV infection.

Nonalcoholic steatohepatitis (NASH) cirrhosis is anticipated to be the major etiological factor for HCC in the future, as the number of NASH cases continues to increase in parallel with the obesity and diabetes epidemics.[13] Several studies support an association between NASH and an increased risk of HCC, although this risk appears to be limited primarily to those with cirrhosis. Patients with NASH, but no cirrhosis, typically have cumulative HCC mortality rates of <1%, whereas those with NASH-related cirrhosis have cumulative HCC incidence rates of 2.4% to 12.8%.[14]

Most recent reports suggest that the incidence of HCC in high- and intermediate-incidence areas may be stabilizing or falling.[2] In China and Taiwan, this is related to more widespread HBV vaccination programs and higher rates of HBV treatment.[15] In Japan and Southern Europe, the decrease in HCC incidence may relate to an aging cohort of patients with HCV infection.[16,17] In contrast, the incidence of HCC in low-incidence areas, such as the United States, is rapidly increasing. In the 10-year period from 1995 to 2004, HCC had the largest increase in incidence among all solid tumors in the United States.[18] The rising incidence of HCC in the United States is related to several factors, but the two most important are growing populations of patients with advanced HCV infection and NASH.[2] In parallel with its rising incidence rate, HCC also has one of the fastest growing death rates among solid tumors. Whereas the prognosis for most solid cancers improved over the 10-year period from 1994 to 2003, the mortality rate for HCC nearly doubled.[7,18]

Surveillance and Early Detection

Because many patients with HCC are asymptomatic when tumors are at an early stage, routine surveillance in patients with cirrhosis is important (Table 1). Although predictive risk models have been created to better define a high-risk subgroup among cirrhotic patients, none have been externally validated or ready for routine use in clinical practice.[19,20] Ultrasound is the most widely used radiological test for HCC surveillance.[21] The sensitivity of ultrasound for early stage HCC is only 63% (95% CI 49% to 76%), meaning more than one-third of all tumors are missed or diagnosed at advanced stages.[22] Although α fetoprotein (AFP) was included as an adjunct surveillance test to ultrasound in prior guidelines, there has been increasing debate regarding its usefulness in surveillance.[23−27] Recent data suggest that AFP may improve the effectiveness of surveillance for detecting early HCC in clinical practice, increasing sensitivity from <50% for ultrasound or AFP alone to nearly 65% when the two tests are combined.[26] Other tumor biomarkers that have been evaluated include des-γ-carboxy prothrombin and the lens culinaris-agglutinin reactive fraction of AFP (APF-L3%)[28]; however, a large multicenter study demonstrated that AFP may be more sensitive for early stage HCC than either of these two biomarkers.[29] Glypican 3,[30,31] GP73,[32] osteopontin,[33] squamous cell carcinoma antigen,[34] human hepatocyte growth factor,[35] and insulin growth factor-1,[36] are examples of other biomarkers that are being evaluated, but data are preliminary and require validation in large cohorts. The field of proteomics may also provide tools to determine other novel serum biomarkers in HCC in the future.[37]

Pathological Features of HCC and Clinical Prognostic Tools

Effective radiological methods can yield a diagnosis of HCC; however, pathological evaluation remains a key aspect of clinical management. Microscopically, HCC tends to resemble normal hepatocytes, depending on the degree of differentiation, and architecture within the tumor can recapitulate normal liver architecture in the early stages, mimicking normal liver cell plates. Most commonly, HCC produces acinar, pseudoglandular, trabecular, and solid growth patterns, often with multiple growth patterns within a single tumor (Figure 1). As the tumor progresses, the preservation of architecture is lost, with crowding and high nuclear to cytoplasmic ratio. When HCC arises in a background of cirrhosis, distinguishing characteristics of the underlying disease are not present sometimes, which is due to altered landmarks and vascular relationships; however, histological changes in the surrounding cirrhotic liver can

Table 1 Patient Populations in Whom Surveillance Is Recommended

Surveillance Recommended
  Asian male hepatitis B carrier older than age 40
  Asian female hepatitis B carrier older than age 50
  African Blacks with hepatitis B
  Hepatitis B carrier with family history of HCC
  Cirrhosis from any etiology
Surveillance Benefits Uncertain
  Asian hepatitis B carriers younger than age 40 (males) or younger than age 50 (females)
  Hepatitis B carriers who contracted infection via horizontal transmission
  Hepatitis C carriers without cirrhosis
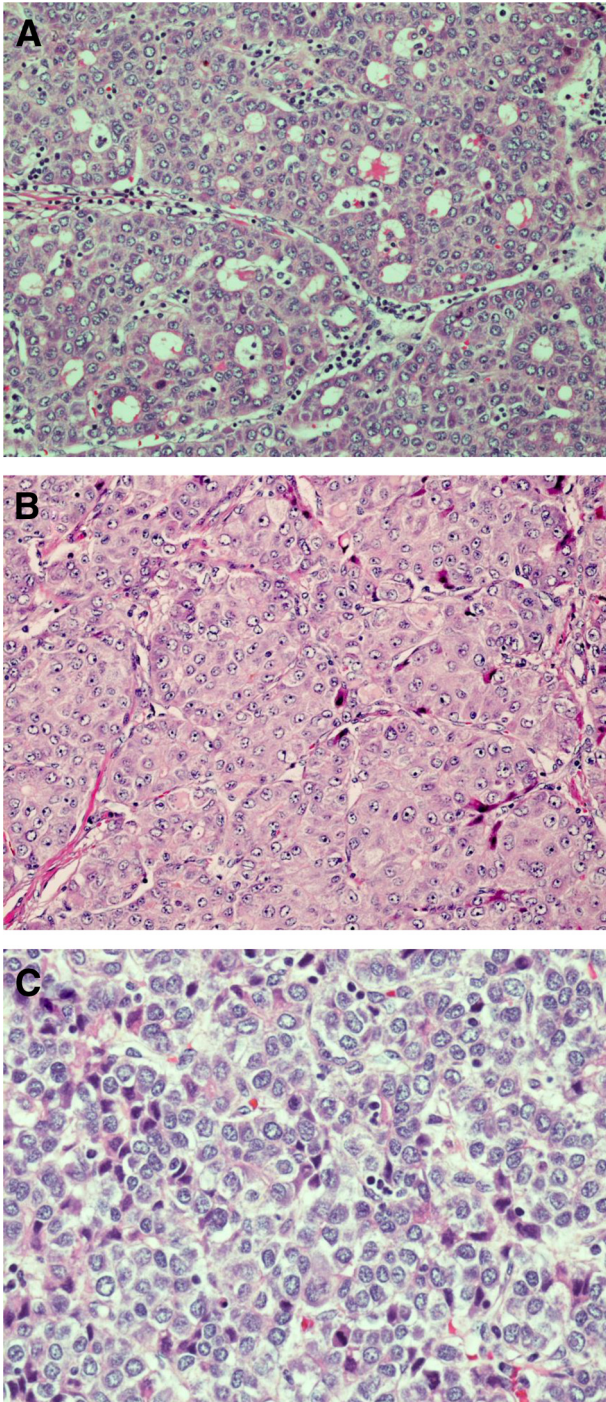 Nonalcoholic fatty liver disease patients without cirrhosis

Figure 1   **A:** H&E staining for hepatocellular carcinoma, pseudoglandular growth pattern. **B:** Hepatocellular carcinoma, trabecular growth pattern. **C:** Hepatocellular carcinoma, solid growth pattern. Original magnification: ×20 (**A**); ×40 (**B** and **C**).

often provide a clue to the etiology of the cirrhosis and HCC. NASH and alcoholic liver disease have several histological similarities, including steatosis, ballooning degeneration of hepatocytes, Mallory-Denk bodies, pericellular fibrosis, and mixed lobular inflammation. Typical histological findings of HCV infection include portal lymphoplasmacytic inflammatory infiltrate, occasionally with prominent lymphoid aggregates, and variable lobular inflammation. Histological findings of HBV can overlap with HCV, but ground glass hepatocytes are a distinctive histological feature that can help distinguish cases of HBV infection. Several recent studies have described a steatohepatitic variant of HCC that can be seen in patients with HCC related to steatohepatitis (NASH and/or alcoholic liver disease).[38–41] This HCC variant is described as having steatohepatitis-like features within the tumor, including steatosis, ballooning degeneration of the malignant hepatocytes, intratumoral pericellular fibrosis, Mallory-Denk bodies, and inflammation (Figure 2). In a study by Salomao et al,[40] 36% of patients who developed HCC in the setting of steatohepatitis were diagnosed as having a steatohepatitic variant of HCC as compared to 1.3% of HCC patients without steatohepatitis. Immunohistochemically, there was diffuse loss of cytoplasmic CK8/18 and an increased number of activated hepatic stellate cells with the steatohepatitic HCC, identical to the pattern seen in the surrounding nonneoplastic liver.[40]
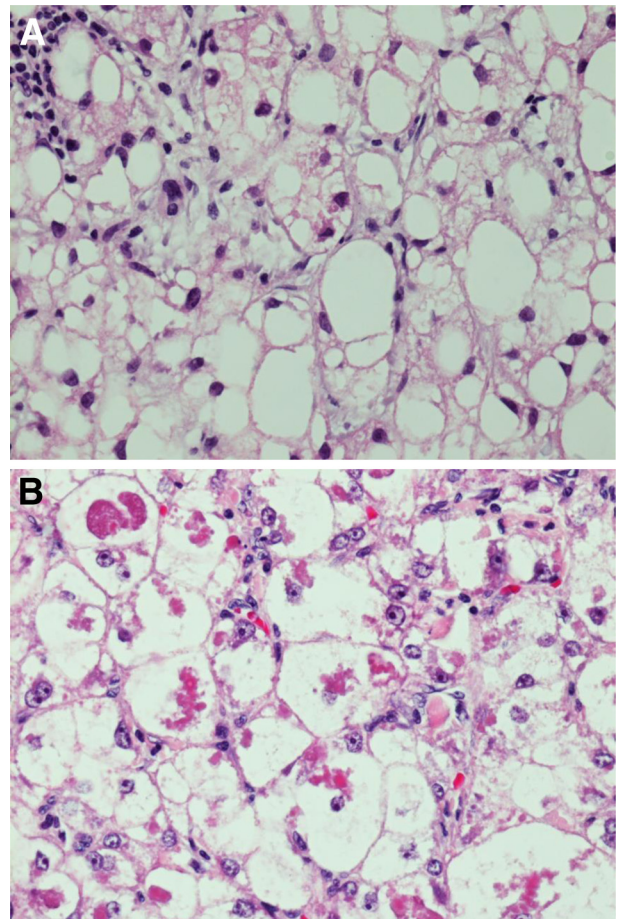

Figure 2   **A:** H&E staining for hepatocellular carcinoma arising in NASH with prominent intratumoral steatosis, chronic inflammation, and rare ballooned tumor cells containing Mallory-Denk bodies. **B:** Hepatocellular carcinoma arising in NASH with ballooned tumor cells containing prominent Mallory-Denk bodies. Original magnification, ×40 (**A** and **B**).

Patients with NASH-related HCC often have less severe liver dysfunction at HCC diagnosis and may have better overall survival after curative treatments than their counterparts with HCV and/or alcohol-related cirrhosis.[42] However, studies specifically evaluating steatohepatitic HCC have not found any difference in prognosis compared to conventional HCC, including similar rates of distant metastases, local recurrence, or overall survival.[40]

Although there is histological variation between HCC cases, these variations are not routinely used in treatment decision-making. In general, treatment decisions are based on the Barcelona Clinical Liver Cancer staging system, which has been validated in several large cohort studies.[43,44] In essence, this staging system incorporates information related to liver function (Child-Turcotte-Pugh Score), performance status, and tumor burden. This staging system is unique in that it has been linked to a treatment algorithm and can be used to triage patients to potentially curative treatments (ie, resection, transplant, ablation) versus chemoembolization versus systemic therapies. It is clear that additional factors could further enhance its prognostic ability, which has spurred the investigation of HCC molecular features that could better portend prognosis or define new opportunities for therapy.

Genetic Underpinnings of HCC

It is clear that diverse etiological stresses play a key role in the etiology of HCC. However, the prevailing view is that liver damage drives aberrant cycles of proliferation in the context of inflamed cirrhotic liver tissue leading to the accumulation of genetic changes that ultimately drive transformation of target cells to HCC (Figure 3).[45] Although conventional targeted analyses of specific markers in the HCC have been performed and have identified key pathways of significance to the etiology,[46,47] unbiased molecular approaches have provided an opportunity to decipher key pathways and genetic events in disease and their connection to the underlying etiologies. Particularly, utilization of gene expression profiling and next generation sequencing technologies provide a portrait of common molecular events that occur in the pathogenesis of HCC.

At present, the sequencing of exons in approximately 100 HCC cases has been performed (Table 2).[48−52] It should be noted that although an important effort from multiple groups, this pales in reference to other diseases, wherein >1000 tumors have been sequenced. However, these studies have yielded a wealth of information in reference to genetic architecture of HCC and key pathways that are likely relevant to the development of HCC.

One of the seminal advantages of next generation sequencing is the ability to define new mediators of hepatocarcinogenesis, and the analyses of data have revealed several key previously unknown features of disease and important new pathways that are likely of high relevance in HCC. An important and often underappreciated aspect of sequencing is the ability to define mutation spectra (eg, C to T transitions) that are particularly prevalent in the disease. Many tumor types have distinct spectra that are associated with disease etiology. For example, lung cancers have C→A, which are specifically associated with smoking,
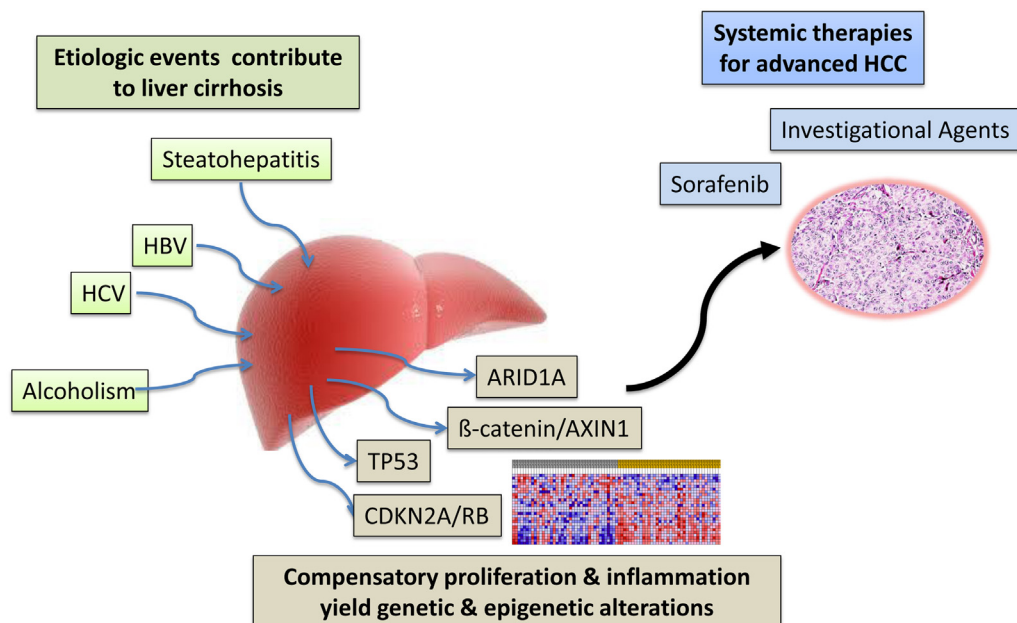
Figure 3   Multiple etiological events drive liver cirrhosis. This results in multiple cycles of compensatory proliferation and inflammation, which can drive the development of genetic and epigenetic alterations. Complex combinations of these events are associated with the development of HCC. Early stage disease can be treated with locoregional therapies, but systemic approaches are relatively limited at present. Multiple investigational drugs are under investigation. HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 2 Studies with Exon Sequencing of HCC Cases

Common mutations	Cases (*n*)	Etiology	References
CTNNB1 (11%)	27	HBV/HCV	50
TP53 (52%)			
ARID1A (19%)			
CTNNB1 (16%)	88	HBV	51
TP53 (35%)			
TP53 (10%)	10	HBV	49
ARID1A (10%)			
ARID2 (10%)			
CTNNB1 (46%)	24	50% alcohol	48
TP53 (13%)		HBV/HCV	
AXIN1 (21%)			
ARID1A (17%)			

whereas melanoma has CC→TT dinucleotide substitutions that would be associated with exposure to solar radiation.[53–55] To date, sequencing has been performed largely on cases with a viral (HBV or HCV) or alcohol-related etiology.[48–52] In this context, HCC has a relatively unique mutation spectra, G→T, which is apparently modified by the etiological basis of disease, with HCC arising in cirrhotic livers exhibiting differential mutational events relative to noncirrhotic livers.[48] However, with the relatively small number of samples, it is difficult to discern if different etiological stresses are associated with specific genetic events. Additionally, to date, no significant cohorts with aflatoxin B1- or NASH-associated tumors have been sequenced; therefore, whether the different mechanisms associated with HCC development will yield distinct genetic alterations remains unknown.

As one may expect, sequencing should identify expected oncogenes and tumor suppressors. The most commonly defined mutated oncogenic driver of HCC is the β-catenin gene (*CTNNB1*).[48–51] This is a validated oncogene that has been previously implicated in HCC pathogenesis from targeted analyses of human tissue and the use of mouse models.[56] Further implicating the importance of this pathway, loss of Axin1 and Axin2, which are negative regulators of β-catenin, are also frequently observed in HCC.[48–51] Similarly, TP53 has been identified as a frequently mutated tumor suppressor in HCC.[48–51] Again, this is consistent with established analysis of human tumor specimens. Surprisingly, TP53 itself is a weak tumor suppressor in mouse models, and largely cooperates with other stresses in suppressing the development of HCC or curtailing the metastatic potential of HCC models.[57,58] These findings reinforce the importance of investigating human tissue to truly understand the underpinnings of human disease. Because exome or whole genome sequencing is a discovery platform, it was an important finding that multiple chromatin modifiers of the SWI/SNF family are associated with HCC.[48–51] Loss of these tumor suppressors is relatively common across multiple solid tumors.[59] Importantly, in such analyses, although Arid1A and Arid2 mutations are particularly prevalent in HCC, multiple genes in the SWI/SNF chromatin remodeling complex are mutated. However, the functional significance of such alterations remains obscure relative to the etiology or progression of HCC. A large number of additional genes involved in discrete carcinogenic processes involved in carcinogenesis were found to be mutated in HCC. For example, composite mutations/loss of cell cycle regulatory genes *CDKN2A* and *RB1*, disruption of genes involved in chromosome stability such as *ATM* and *MLH1*, and genes that mediate epigenetic regulation, such as *MLL3* and *MLL*, have all been found to be mutated in HCC.[48–51] Although these data yield some insight into the genetics of HCC, the lack of commonality between individual cancer cases is most striking. This contrasts with tumors like pancreatic cancer in which veritably of all cases harbor well-known oncogenic drivers (ie, K-ras). These data underline one of the unique features of HCC in that it is highly heterogeneous. Given this same heterogeneity it remains unclear how such genetic findings will yield actionable insights on which disease treatment can be modified to improve patient outcomes.

Gene Expression Profiling Prognostic Markers and Pathways

In contrast with the seemingly infinite diversity of HCC as shown by sequencing, gene expression profiling approaches monitoring changes in RNA levels on microarray platforms have defined a limited series of HCC subtypes (Table 3).

Table 3 HCC Subtypes Identified by Gene Expression Profiling Approaches

Subtypes	Genes/Processes	Clinical endpoint	References
A and B	Multiple/proliferation	Overall survival	61
CIN: high and low	Proliferation	Overall survival	64
G1-G6	Multiple/proliferation	Overall survival	67
RB-loss: high and low	Proliferation	Overall survival	63
A, B, and C	Multiple/proliferation	Overall survival	65
65 genes	Multiple	Overall survival	72
5-gene score	HN1, RAN, RAMP3, KRT19, and TAF9	Overall survival	70
		End-stage disease	
186-gene signature	Nontumor liver	Overall survival	69
		Risk of recurrence	

CIN, chromosome instability signature.

Early work from Dr. Thorgeirrson's group defined gene expression changes in HCC cases related to proliferation and other core features of disease that were associated with prognosis.[60–63] These findings were recapitulated from numerous groups demonstrating that tumors with elevated expression of proliferation-associated genes were prognostic for poor outcome dependent on methodology.[34,63–66] Additional analyses served to define subgroups. Specifically, HCC can be classified into three or six subtypes based on gene expression profiling.[65,67] These groups are consistent across multiple independent cohorts and have differential overall prognosis.[65] This work was similar to that performed in breast cancer[68] and is important for clarifying intrinsically different forms of HCC that have distinct prognosis. Such multigene signatures have been distilled to inform progression of early stage disease and vascular invasion.[31,69–72] Most recently, extensive analysis of clinical specimens by gene expression profiling defined a 5-gene signature.[70] This signature was effective in both training and validation sets and outperformed other signatures that have been previously identified for determining the risk of recurrence and death after disease resection. Analysis of the nontumor liver tissue also provides important prognostic information. A 186-gene signature is associated with poor prognosis of early stage disease and risk of disease progression in the cirrhotic liver.[69] Presumably, this is because the tissue is reflective of the carcinogenic milieu within the liver, and thus it is associated with risk of poor clinical outcome. Although multiple signatures appear prognostic in retrospective analysis, there remain no established predictive markers that have been shown to improve patient treatment. Thus, although there are newly defined subtypes of HCC based on gene expression profiles, these markers have yet to yield directed treatments for HCC.

Targeted Therapeutic Interventions: A Work in Progress

Despite substantial and accelerated research in the area of HCC, the 5-year survival for advanced disease remains <10%.[73–75] Localized disease can be treated with ablative therapies, surgical resection, or transplantion.[75–77] However, many cases present at the advanced stage or the patient is a poor candidate for such interventions. Thus, substantial clinical research has been conducted to provide improved treatment for HCC with systemic therapies. Phase III trials have evaluated multiple therapeutic modalities, including tamoxifen, chemotherapy, and interferon, all with negative outcomes.[76,78,79] The lack of benefit with multiple chemotherapy regimens makes HCC somewhat unique in cancer by having no standard cytotoxic therapy, and indicates that HCC must be treated by other targeted agents.[80–82] The only drug approved for advanced HCC is the multikinase inhibitor sorafenib. In HCC, sorafenib functions as a cytostatic agent that provides an approximate 3-month improvement in survival versus placebo control based on large randomized phase III trial versus placebo.[83] Despite the positive impact on survival, HCC remains a classical therapy recalcitrant disease for which new interventions are needed.

Multiple ongoing phase II and phase III trials support the possible development of new treatment opportunities for advanced HCC.[78,84] The majority of phase II trials represent approaches to define positive effect of treatment with progression-free survival as the primary endpoint.[85,86] These studies build off of the clinical outcomes with sorafenib and are often conducted in the second line (after sorafenib failure) or as a first-line agent in combination with sorafenib.[84] A number of agents have shown promise in this context including brivanib and bevacizumab-erlotinib.[87–90] Because of the advanced nature of HCC and the underlying liver disease and underlying liver disease associated with late stage HCC, the outcomes have been relatively modest. Interestingly, sorafenib, brivanib, and bevacizumab all targeted VEGF signaling, suggesting that this may be an important therapeutic node in HCC. Based on the identification of multiple additional key pathways disrupted in HCC, trials have been rationally directed to target common oncogenic events. For example, with the key role of Met signaling in HCC, the drug tivantinib has been investigated in a randomized phase II trial.[91,92] Similarly, given the frequent loss of CDKN2A and deregulation of the retinoblastoma tumor suppressor pathway, the CDK4/6 inhibitor PD-0332991 is being tested in advanced HCC (*http://clinicaltrials.gov*, Clinical Trial NCT01356628). These trials and further multiple, additional trials will likely shed light on agents that have potential usefulness in HCC. A critical aspect of such targeted therapies is the importance of defining features of disease that underlie sensitivity to the agent. For example, in retrospective analysis, tivantinib is particularly effective against HCC, which has a high expression of Met.[91,92] Therefore, it will be important to leverage the molecular analyses of HCC to delineate specific subtypes of HCC or individual cases that would be particularly responsive to a given therapeutic regimen.

Challenges and Future Directions

HCC represents a particular challenge for which there is multiple opportunities to change the large burden of disease and terrible prognosis.

Prevention

Because etiological features of HCC are very well-defined, it represents a disease for which preventive strategies could be particularly effective. Ostensibly, these etiologies can be ultimately controlled, thereby substantially reducing the number of individuals at high risk for HCC. The decreasing incidence of HCC in Asia speaks to the potential benefits and promise of preventive measures, such as HBV

vaccination and treatment.[93] Although a vaccine for HCV does not exist, successful treatment has been associated with significant reductions in HCC risk.[94] The introduction of interferon-free treatment regimens, with better success rates and lower toxicity rates, may further expand HCV treatment rates and help to reduce the future burden of HCC.[95] Given the increasing prevalence of NASH-related HCC, studies assessing the potential impact of weight loss, either via diet and exercise or bariatric surgery, are necessary. Finally, larger studies assessing the potential preventive benefit of diet, coffee, and statins are necessary.[96,97]

Early Detection

Because the etiological factors of HCC can be defined relatively easily in the clinic, it is surprising that the diagnosis of HCC often occurs at such a late stage.[18] This failure is related to several reasons, including underutilization of surveillance, delayed follow-up of surveillance tests, and suboptimal effectiveness of surveillance tests. Several studies have demonstrated that <20% of patients with cirrhosis receive HCC surveillance, as recommended by guidelines.[98–100] Underutilization of HCC surveillance is related to multiple failure points, including under-recognition of liver disease, under-recognition of cirrhosis, and physicians failing to order HCC surveillance in patients with known cirrhosis, highlighting a need for multifaceted interventions to improve cirrhosis recognition and facilitate HCC surveillance testing.[101] However, a secondary analysis of the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) trial suggested that the most common reason for late stage tumor presentation is related to poor sensitivity of currently available surveillance tools.[102] Therefore, it is critically important to develop markers that are easily used that have a high sensitivity and specificity for the detection of early stage disease. Such markers could then provide the trigger for radiological imaging to identify early stage disease in which resection or ablative therapies can be more effective.

Fully Understanding the Genetic Diversity

For HCC, sequencing analysis has served to provide a better understanding of the tumor genetics. However, these data have also demonstrated that no HCC tumor is alike, and only a minority of cases has a mutation that would immediately provoke a specific therapeutic approach. Therefore, the challenge is to understand how genetics can be used to provide a road map for the treatment of HCC.

Dissecting the Therapeutic Sensitivities of HCC Subtypes

At present, HCC cases are treated similarly with little consideration of molecular subtypes or markers that could be relevant to prognosis or therapeutic sensitivities. There is clearly an opportunity to define markers predictive of response to specific agents to begin refining the treatment paradigm for HCC from a one size fits all to one of more precision-guided therapy. The emerging trials with tivantinib will provide the first indication that stratifying patients to specific treatment regimens will perhaps improve care.[91]

Implementing More Effective Treatment

The dismal prognosis of advanced HCC provides a seminal opportunity for improved treatment options. The plethora of ongoing early stage trials provides hope for more effective regimens, although it will be critically important to consider the incredible diversity of HCC when investigating therapeutic response. Clinicians should be cognizant of the opportunity that is provided by analyzing tissue from such trials to better inform future clinical interventions and to avoid making broad conclusions on an unselected patient population, wherein the expectation should be likely that only a subset of patients would experience a favorable response to the intervention.

References

1. El-Serag HB, Rudolph KL: Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007, 132:2557–2576
2. El-Serag HB: Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012, 142:1264–1273.e1
3. Beasley R: Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 1988, 61:1942–1956
4. Yu MW, Chang HC, Liaw YF, Lin SM, Lee SD, Liu CJ, Chen PJ, Hsiao TJ, Lee PH, Chen CJ: Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. J Natl Cancer Inst 2000, 92:1159–1164
5. Kew MC, Macerollo P: Effect of age on the etiologic role of the hepatitis B virus in hepatocellular carcinoma in blacks. Gastroenterology 1988, 94:439–442
6. Qian GS, Ross RK, Yu MC, Yuan JM, Gao YT, Henderson BE, Wogan GN, Groopman JD: A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. Cancer Epidemiol Biomarkers Prev 1994, 3:3–10
7. El-Serag HB: Hepatocellular carcinoma: recent trends in the United States. Gastroenterology 2004, 127:S27–S34
8. Donato F, Boffetta P, Puoti M: A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 1998, 75:347–354
9. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassini R, Noventa F, Schalm SW, Realdi G: Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997, 112:463–472
10. Sun CA, Wu DM, Lin CC, Lu SN, You SL, Wang LY, Wu MH, Chen CJ: Incidence and cofactors of hepatitis C virus-related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan. Am J Epidemiol 2003, 157:674–682
11. Adami HO, Hsing AW, McLaughlin JK, Trichopoulos D, Hacker D, Ekbom A, Persson I: Alcoholism and liver cirrhosis in the etiology of primary liver cancer. Int J Cancer 1992, 51:898–902
12. Hassan MM, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P, Patt YZ: Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002, 36:1206–1213

13. Starley BQ, Calcagno CJ, Harrison SA: Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology 2010, 51:1820−1832

14. White DL, Kanwal F, El-Serag HB: Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol 2012, 10: 1342−1359.e2

15. Tajiri H, Tanaka H, Brooks S, Takano T: Reduction of hepatocellular carcinoma in childhood after introduction of selective vaccination against hepatitis B virus for infants born to HBV carrier mothers. Cancer Causes Control 2011, 22:523−527

16. Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T, Alter HJ: A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. Proc Natl Acad Sci U S A 2002, 99:15584−15589

17. Umemura T, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K: Epidemiology of hepatocellular carcinoma in Japan. J Gastroenterol 2009, 44(Suppl 19):102−107

18. Altekruse SF, McGlynn KA, Reichman ME: Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009, 27:1485−1491

19. Singal AG, Mukherjee A, Elmunzer BJ, Higgins PDR, Lok AS, Zhu J, Marrero JA, Waljee AK: Machine learning algorithms outperform conventional regression models in predicting development of hepatocellular carcinoma. Am J Gastroenterol 2013, 108:1723−1730

20. Yuen MF, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, But DY, Chan AO, Wong BC, Mizokami M, Lai CL: Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol 2009, 50:80−88

21. Chalasani N, Said A, Ness R, Hoen H, Lumeng L: Screening for hepatocellular carcinoma in patients with cirrhosis in the United States: results of a national survey. Am J Gastroenterol 1999, 94: 2224−2229

22. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA: Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009, 30:37−47

23. Bruix J, Sherman M: Management of hepatocellular carcinoma: an update. Hepatology 2010, 53:1−35

24. Lee E, Edward S, Singal AG, Lavieri MS, Volk M: Improving screening for hepatocellular carcinoma by incorporating data on levels of alpha-fetoprotein, over time. Clin Gastroenterol Hepatol 2013, 11:437−440

25. Marrero JA, El-Serag HB: Alpha-fetoprotein should be included in the hepatocellular carcinoma surveillance guidelines of the American Association for the Study of Liver Diseases. Hepatology 2011, 53: 1060−1061

26. Singal AG, Conjeevaram HS, Volk ML, Fu S, Fontana RJ, Askari F, Su GL, Lok AS, Marrero JA: Effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis. Cancer Epidemiol Biomarkers Prev 2012, 21:793−799

27. Gopal P, Yopp AC, Waljee AK, Chiang J, Nehra M, Kandunoori P, Singal AG: Factors that affect accuracy of alpha-fetoprotein test in detection of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2013, http://dx.doi.org/10.1016/j.cgh.2013.09. 053 [Epub ahead of print]

28. Sato Y, Nakata K, Kato Y, Shima M, Ishii N, Koji T, Taketa K, Endo Y, Nagataki S: Early recognition of hepatocellular carcinoma based on altered profiles of alpha-fetoprotein. N Engl J Med 1993, 328:1802−1806

29. Marrero JA, Feng Z, Wang Y, Nguyen MH, Befeler AS, Roberts LR, Reddy KR, Harnois D, Llovet JM, Normolle D, Dalhgren J, Chia D, Lok AS, Wagner PD, Srivastava S, Schwartz M: Alpha-fetoprotein, Des-gamma Carboxyprothrombin, and Lectin-Bound Alpha-fetoprotein in Early Hepatocellular Carcinoma AFP, DCP, and AFP-L3 in Hepatocellular carcinoma. Gastroenterology 2009, 137:110−118

30. Capurro M, Wanless IR, Sherman M, Deboer G, Shi W, Miyoshi E, Filmus J: Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma. Gastroenterology 2003, 125:89−97

31. Llovet JM, Chen Y, Wurmbach E, Roayaie S, Fiel MI, Schwartz M, Thung SN, Khitrov G, Zhang W, Villanueva A, Battiston C, Mazzaferro V, Bruix J, Waxman S, Friedman SL: A molecular signature to discriminate dysplastic nodules from early hepatocellular carcinoma in HCV cirrhosis. Gastroenterology 2006, 131:1758−1767

32. Marrero JA, Romano PR, Nikolaeva O, Steel L, Mehta A, Fimmel CJ, Comunale MA, D'Amelio A, Lok AS, Block TM: GP73, a resident Golgi glycoprotein, is a novel serum marker for hepatocellular carcinoma. J Hepatol 2005, 43:1007−1012

33. Shang S, Plymoth A, Ge S, Feng Z, Rosen HR, Sangrajrang S, Hainaut P, Marrero JA, Beretta L: Identification of osteopontin as a novel marker for early hepatocellular carcinoma. Hepatology 2012, 55:483−490

34. Beneduce L, Castaldi F, Marino M, Quarta S, Ruvoletto M, Benvegnu L, Calabrese F, Gatta A, Pontisso P, Fassina G: Squamous cell carcinoma antigen-immunoglobulin M complexes as novel biomarkers for hepatocellular carcinoma. Cancer 2005, 103:2558−2565

35. Yamagami H, Moriyama M, Tanaka N, Arakawa Y: Detection of serum and intrahepatic human hepatocyte growth factor in patients with type C liver diseases. Intervirology 2001, 44:36−42

36. Mazziotti G, Sorvillo F, Morisco F, Carbone A, Rotondi M, Stornaiuolo G, Precone DF, Cioffi M, Gaeta GB, Caporaso N, Carella C: Serum insulin-like growth factor I evaluation as a useful tool for predicting the risk of developing hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a prospective study. Cancer 2002, 95:2539−2545

37. Chignard N, Beretta L: Proteomics for hepatocellular carcinoma marker discovery. Gastroenterology 2004, 127:S120−S125

38. Alexander J, Torbenson M, Wu TT, Yeh MM: Non-alcoholic fatty liver disease contributes to hepatocarcinogenesis in non-cirrhotic liver: a clinical and pathological study. J Gastroenterol Hepatol 2013, 28:848−854

39. Salomao M, Yu WM, Brown RS Jr., Emond JC, Lefkowitch JH: Steatohepatitic hepatocellular carcinoma (SH-HCC): a distinctive histological variant of HCC in hepatitis C virus-related cirrhosis with associated NAFLD/NASH. Am J Surg Pathol 2010, 34:1630−1636

40. Salomao M, Remotti H, Vaughan R, Siegel AB, Lefkowitch JH, Moreira RK: The steatohepatitic variant of hepatocellular carcinoma and its association with underlying steatohepatitis. Hum Pathol 2012, 43:737−746

41. Jain D, Nayak NC, Kumaran V, Saigal S: Steatohepatitic hepatocellular carcinoma, a morphologic indicator of associated metabolic risk factors: a study from India. Arch Pathol Lab Med 2013, 137:961−966

42. Reddy SK, Steel JL, Chen HW, DeMateo DJ, Cardinal J, Behari J, Humar A, Marsh JW, Geller DA, Tsung A: Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. Hepatology 2012, 55: 1809−1819

43. Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, Lok AS: Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Hepatology 2005, 41:707−716

44. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, Neri D, Boccagni P, Srsen N, D'Amico F, Ciarleglio FA, Bridda A, D'Amico DF: Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006, 44:723−731

45. Farazi PA, DePinho RA: Hepatocellular carcinoma pathogenesis: from genes to environment. Nat Rev Cancer 2006, 6:674−687

46. Buendia MA: Genetics of hepatocellular carcinoma. Semin Cancer Biol 2000, 10:185−200

47. Bioulac-Sage P, Laurent-Puig P, Balabaud C, Zucman-Rossi J: Genetic alterations in hepatocellular adenomas. Hepatology 2003, 37: 480; author reply -1

48. Guichard C, Amaddeo G, Imbeaud S, Ladeiro Y, Pelletier L, Maad IB, Calderaro J, Bioulac-Sage P, Letexier M, Degos F,

Clement B, Balabaud C, Chevet E, Laurent A, Couchy G, Letouze E, Calvo F, Zucman-Rossi J: Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. Nat Genet 2012, 44:694−698

49. Huang J, Deng Q, Wang Q, Li KY, Dai JH, Li N, Zhu ZD, Zhou B, Liu XY, Liu RF, Fei QL, Chen H, Cai B, Zhou B, Xiao HS, Qin LX, Han ZG: Exome sequencing of hepatitis B virus-associated hepatocellular carcinoma. Nat Genet 2012, 44:1117−1121

50. Fujimoto A, Totoki Y, Abe T, Boroevich KA, Hosoda F, Nguyen HH, et al: Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. Nat Genet 2012, 44:760−764

51. Kan Z, Zheng H, Liu X, Li S, Barber TD, Gong Z, et al: Whole-genome sequencing identifies recurrent mutations in hepatocellular carcinoma. Genome Res 2013, 23:1422−1433

52. Nakagawa H, Shibata T: Comprehensive genome sequencing of the liver cancer genome. Cancer Lett 2013, 340:234−240

53. Imielinski M, Berger AH, Hammerman PS, Hernandez B, Pugh TJ, Hodis E, et al: Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell 2012, 150:1107−1120

54. Krauthammer M, Kong Y, Ha BH, Evans P, Bacchiocchi A, McCusker JP, Cheng E, Davis MJ, Goh G, Choi M, Ariyan S, Narayan D, Dutton-Regester K, Capatana A, Holman EC, Bosenberg M, Sznol M, Kluger HM, Brash DE, Stern DF, Materin MA, Lo RS, Mane S, Ma S, Kidd KK, Hayward NK, Lifton RP, Schlessinger J, Boggon TJ, Halaban R: Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. Nat Genet 2012, 44:1006−1014

55. Nikolaev SI, Rimoldi D, Iseli C, Valsesia A, Robyr D, Gehrig C, Harshman K, Guipponi M, Bukach O, Zoete V, Michielin O, Muehlethaler K, Speiser D, Beckmann JS, Xenarios I, Halazonetis TD, Jongeneel CV, Stevenson BJ, Antonarakis SE: Exome sequencing identifies recurrent somatic MAP2K1 and MAP2K2 mutations in melanoma. Nat Genet 2012, 44:133−139

56. Harada N, Oshima H, Katoh M, Tamai Y, Oshima M, Taketo MM: Hepatocarcinogenesis in mice with beta-catenin and Ha-ras gene mutations. Cancer Res 2004, 64:48−54

57. McClendon AK, Dean JL, Ertel A, Fu Z, Rivadeneira DB, Reed CA, Bourgo RJ, Witkiewicz A, Addya S, Mayhew CN, Grimes HL, Fortina P, Knudsen ES: RB and p53 cooperate to prevent liver tumorigenesis in response to tissue damage. Gastroenterology 2011, 141:1439−1450

58. Lewis BC, Klimstra DS, Socci ND, Xu S, Koutcher JA, Varmus HE: The absence of p53 promotes metastasis in a novel somatic mouse model for hepatocellular carcinoma. Mol Cell Biol 2005, 25: 1228−1237

59. Kadoch C, Hargreaves DC, Hodges C, Elias L, Ho L, Ranish J, Crabtree GR: Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. Nat Genet 2013, 45:592−601

60. Lee JS, Thorgeirsson SS: Functional and genomic implications of global gene expression profiles in cell lines from human hepatocellular cancer. Hepatology 2002, 35:1134−1143

61. Lee JS, Chu IS, Heo J, Calvisi DF, Sun Z, Roskams T, Durnez A, Demetris AJ, Thorgeirsson SS: Classification and prediction of survival in hepatocellular carcinoma by gene expression profiling. Hepatology 2004, 40:667−676

62. Lee JS, Thorgeirsson SS: Genome-scale profiling of gene expression in hepatocellular carcinoma: classification, survival prediction, and identification of therapeutic targets. Gastroenterology 2004, 127: S51−S55

63. Mayhew CN, Carter SL, Fox SR, Sexton CR, Reed CA, Srinivasan SV, Liu X, Wikenheiser-Brokamp K, Boivin GP, Lee JS, Aronow BJ, Thorgeirsson SS, Knudsen ES: RB loss abrogates cell cycle control and genome integrity to promote liver tumorigenesis. Gastroenterology 2007, 133:976−984

64. Carter SL, Eklund AC, Kohane IS, Harris LN, Szallasi Z: A signature of chromosomal instability inferred from gene expression profiles predicts clinical outcome in multiple human cancers. Nat Genet 2006, 38:1043−1048

65. Hoshida Y, Nijman SM, Kobayashi M, Chan JA, Brunet JP, Chiang DY, Villanueva A, Newell P, Ikeda K, Hashimoto M, Watanabe G, Gabriel S, Friedman SL, Kumada H, Llovet JM, Golub TR: Integrative transcriptome analysis reveals common molecular subclasses of human hepatocellular carcinoma. Cancer Res 2009, 69:7385−7392

66. Villanueva A, Hoshida Y, Battiston C, Tovar V, Sia D, Alsinet C, Cornella H, Liberzon A, Kobayashi M, Kumada H, Thung SN, Bruix J, Newell P, April C, Fan JB, Roayaie S, Mazzaferro V, Schwartz ME, Llovet JM: Combining clinical, pathology, and gene expression data to predict recurrence of hepatocellular carcinoma. Gastroenterology 2011, 140:1501−1512.e2

67. Boyault S, Rickman DS, de Reynies A, Balabaud C, Rebouissou S, Jeannot E, Herault A, Saric J, Belghiti J, Franco D, Bioulac-Sage P, Laurent-Puig P, Zucman-Rossi J: Transcriptome classification of HCC is related to gene alterations and to new therapeutic targets. Hepatology 2007, 45:42−52

68. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO, Botstein D: Molecular portraits of human breast tumours. Nature 2000, 406:747−752

69. Hoshida Y, Villanueva A, Sangiovanni A, Sole M, Hur C, Andersson KL, Chung RT, Gould J, Kojima K, Gupta S, Taylor B, Crenshaw A, Gabriel S, Minguez B, Iavarone M, Friedman SL, Colombo M, Llovet JM, Golub TR: Prognostic gene expression signature for patients with hepatitis C-related early-stage cirrhosis. Gastroenterology 2013, 144:1024−1030

70. Nault JC, De Reynies A, Villanueva A, Calderaro J, Rebouissou S, Couchy G, Decaens T, Franco D, Imbeaud S, Rousseau F, Azoulay D, Saric J, Blanc JF, Balabaud C, Bioulac-Sage P, Laurent A, Laurent-Puig P, Llovet JM, Zucman-Rossi J: A hepatocellular carcinoma 5-gene score associated with survival of patients after liver resection. Gastroenterology 2013, 145:176−187

71. Minguez B, Hoshida Y, Villanueva A, Toffanin S, Cabellos L, Thung S, Mandeli J, Sia D, April C, Fan JB, Lachenmayer A, Savic R, Roayaie S, Mazzaferro V, Bruix J, Schwartz M, Friedman SL, Llovet JM: Gene-expression signature of vascular invasion in hepatocellular carcinoma. J Hepatol 2011, 55:1325−1331

72. Kim SM, Leem SH, Chu IS, Park YY, Kim SC, Kim SB, Park ES, Lim JY, Heo J, Kim YJ, Kim DG, Kaseb A, Park YN, Wang XW, Thorgeirsson SS, Lee JS: Sixty-five gene-based risk score classifier predicts overall survival in hepatocellular carcinoma. Hepatology 2012, 55:1443−1452

73. Bruix J, Llovet JM: Major achievements in hepatocellular carcinoma. Lancet 2009, 373:614−616

74. Olsen SK, Brown RS, Siegel AB: Hepatocellular carcinoma: review of current treatment with a focus on targeted molecular therapies. Therap Adv Gastroenterol 2010, 3:55−66

75. Forner A, Llovet JM, Bruix J: Hepatocellular carcinoma. Lancet 2012, 379:1245−1255

76. de Lope CR, Tremosini S, Forner A, Reig M, Bruix J: Management of HCC. J Hepatol 2012, 56(Suppl 1):S75−S87

77. Rossi L, Zoratto F, Papa A, Iodice F, Minozzi M, Frati L, Tomao S: Current approach in the treatment of hepatocellular carcinoma. World J Gastrointest Oncol 2010, 2:348−359

78. Chua CW, Choo SP: Targeted therapy in hepatocellular carcinoma. Int J Hepatol 2011, 2011:348297

79. Worns MA, Weinmann A, Schuchmann M, Galle PR: Systemic therapies in hepatocellular carcinoma. Dig Dis 2009, 27:175−188

80. Llovet JM, Bruix J: Molecular targeted therapies in hepatocellular carcinoma. Hepatology 2008, 48:1312−1327

81. Llovet JM, Bruix J: Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol 2008, 48(Suppl 1): S20−S37

82. Finn RS: Development of molecularly targeted therapies in hepatocellular carcinoma: where do we go now? Clin Cancer Res 2010, 16: 390−397

83. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J, Group SIS: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008, 359:378−390

84. Thomas MB, Jaffe D, Choti MM, Belghiti J, Curley S, Fong Y, Gores G, Kerlan R, Merle P, O'Neil B, Poon R, Schwartz L, Tepper J, Yao F, Haller D, Mooney M, Venook A: Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 2010, 28:3994−4005

85. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, Sherman M, Schwartz M, Lotze M, Talwalkar J, Gores GJ: Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008, 100:698−711

86. Llovet JM, Bruix J: Testing molecular therapies in hepatocellular carcinoma: the need for randomized phase II trials. J Clin Oncol 2009, 27:833−835

87. Finn RS, Kang YK, Mulcahy M, Polite BN, Lim HY, Walters I, Baudelet C, Manekas D, Park JW: Phase II, open-label study of brivanib as second-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2012, 18:2090−2098

88. Park JW, Finn RS, Kim JS, Karwal M, Li RK, Ismail F, Thomas M, Harris R, Baudelet C, Walters I, Raoul JL: Phase II, open-label study of brivanib as first-line therapy in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2011, 17:1973−1983

89. Thomas MB, Chadha R, Glover K, Wang X, Morris J, Brown T, Rashid A, Dancey J, Abbruzzese JL: Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. Cancer 2007, 110:1059−1067

90. Thomas MB, Morris JS, Chadha R, Iwasaki M, Kaur H, Lin E, Kaseb A, Glover K, Davila M, Abbruzzese J: Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. J Clin Oncol 2009, 27:843−850

91. Santoro A, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, Van Vlierberghe H, Trojan J, Kolligs FT, Weiss A, Miles S, Gasbarrini A, Lencioni M, Cicalese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Personeni N, Hassoun Z, Abbadessa G, Schwartz B, Von Roemeling R, Lamar ME, Chen Y, Porta C: Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 2013, 14:55−63

92. Trojan J, Zeuzem S: Tivantinib in hepatocellular carcinoma. Expert Opin Investig Drugs 2013, 22:141−147

93. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, Shau WY, Chen DS: Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997, 336:1855−1859

94. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS: A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010, 8:280−288. 288.e1

95. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R, Reindollar R, Rustgi V, McPhee F, Wind-Rotolo M, Persson A, Zhu K, Dimitrova DI, Eley T, Guo T, Grasela DM, Pasquinelli C: Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med 2012, 366:216−224

96. Bravi F, Bosetti C, Tavani A, La Vecchia C: Coffee drinking and hepatocellular carcinoma: an update. Hepatology 2009, 50:1317−1318

97. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W: Statins Are Associated With a Reduced Risk of Hepatocellular Cancer: A Systematic Review and Meta-analysis. Gastroenterology 2013, 144: 323−332

98. Davila JA, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z, El-Serag HB: Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med 2011, 154:85−93

99. Singal AG, Yopp A, SS C, Packer M, Lee WM, Tiro JA: Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. J Gen Intern Med 2012, 27:861−867

100. Singal AG, Yopp A, Gupta S, Skinner CS, Halm EA, Okolo E, Nehra M, Lee WM, Marrero JA, Tiro JA: Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prevent Res 2012, 5:1124−1130

101. Singal AG, Tiro JA, Gupta S: Improving hepatocellular carcinoma screening: applying lessons from colorectal cancer screening. Clin Gastroenterol Hepatol 2013, 11:472−477

102. Singal AG, Nehra M, Adams-Huet B, Yopp AC, Tiro JA, Marrero JA, Lok AS, Lee WM: Detection of hepatocellular carcinoma at advanced stages among patients in the HALT-C trial: where did surveillance fail? Am J Gastroenterol 2013, 108:425−432