Updates in the Management of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death, and its increasing incidence worldwide is a cause for concern. Fortunately, advances in diagnostic and therapeutic approaches have contributed to earlier detection and treatment. As cancer epidemiology studies continue to elucidate the natural history of liver diseases, greater understanding of HCC has led to improved risk stratification and earlier enrollment of high-risk patients in cancer screening and surveillance programs. Improved survival rates among HCC patients also reflect significant advances in available treatment options. Advances in surgical techniques are pushing the boundaries of resection for localized disease, and progress in the field of transplantation has led to refinements in listing criteria and improved post-transplantation outcomes. The evolving field of locoregional therapies—including percutaneous ablation and transarterial chemoembolization—continues to provide novel therapeutic options that can be used in place of, or in addition to, surgical approaches. Recent advances in systemic multikinase inhibitor therapies have also demonstrated significant benefits for advanced-stage disease, and these therapies also show promise as adjuvant treatments for earlier-stage disease. This article provides an update on the management of HCC, with a focus on revised guidelines for screening and an in-depth discussion of emerging novel therapies.

Hepatocellular carcinoma (HCC) ranks among the most common cancers worldwide and is one of the leading causes of cancer-related death.[1-3] Over the last 3 decades, the age-adjusted incidence of liver cancer has risen from 1.6 per 100,000 individuals to 4.6 per 100,000 individuals, with the greatest increase occurring among American Indians and Alaskan natives, followed by blacks, whites, and Hispanics.[4] The incidence of HCC will likely continue to rise as the hepatitis C epidemic reaches maturity and nonalcoholic steatohepatitis becomes more prevalent in the United States.

The clinical evaluation and management of HCC require a comprehensive, multidisciplinary approach that involves cancer surveillance and consideration of both surgical and medical therapies.

The implementation of such an approach has resulted in increased survival rates for HCC.[3-8] In addition, the underlying etiology of HCC affects the optimal time at which to initiate cancer surveillance, and recent updates by the American Association for the Study of Liver Diseases (AASLD) have better defined at-risk groups for which routine HCC screening is recommended.[1]

The therapeutic approach for HCC can vary widely depending on the extent of disease: from potentially curative surgical resection of small localized tumors to liver transplantation or newer biologic therapies for more advanced disease. Advances in the utilization of nonsurgical invasive therapies, such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE), also continue to play a vital role in the management of pre- and peri-operative transplant patients.[1,2,5-8] The current article focuses on recent updates in the management of HCC, with an emphasis on new therapeutic advances.

Screening and Surveillance

The initiation of surveillance for HCC involves identifying at-risk populations that would benefit from cancer screening. The underlying disease process (eg, hepatitis B virus [HBV] or hepatitis C virus [HCV] infection or cirrhosis secondary to alcoholic liver disease) can help define an individual's cancer risk. In an attempt to better formalize cancer surveillance algorithms, the AASLD recently updated its recommendations for HCC screening.[1]

Among patients with cirrhosis secondary to HBV infection, the incidence of HCC is reported to be 2.5% per year, clearly warranting routine cancer surveillance in this population.[9-13] Among HBV carriers without cirrhosis, however, the benefit of routine cancer screening is less clear. The overall malignancy risk among this noncirrhotic cohort is lower, with an incidence of 0.4–0.6% per year; however, data suggest that Asian patients remain at high risk of HCC despite a low-risk DNA replication status (hepatitis B envelope [HBe]-antibody positivity), perhaps because many of these individuals become infected at birth or during early childhood.[11-16] In contrast, the loss of surface antigen or the development of anti-HBe positivity among non-Asian or white populations seems to correlate with a significant decline in malignancy risk.[17,18] Epidemiologic studies also demonstrate significantly higher cancer risk among Africans with chronic HBV.[13] Whether this increased risk persists in blacks born outside of Africa is unclear.

While race and ethnicity help to guide HCC screening programs, several additional factors can impact the potential for malignancy among patients with chronic HBV infection. Patients with a family history of HCC are at increased risk of developing cancer, particularly if the affected family member is a first-degree relative; thus, these individuals can benefit from earlier enrollment in HCC surveillance programs. However, the exact age at which to start surveillance remains unclear, and this decision should reflect any other risk factors that may be present.

Because persistent inflammatory activity demonstrated on liver histology and elevation in liver enzyme levels also correspond with increased cancer risk, HCC screening should be initiated in patients with these findings.[13] In addition, the impact of HBV DNA levels on cancer risk has been investigated in the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in HBV study, a large, prospective, cohort study in Taiwan.[19] This study demonstrated a dose-response relationship between elevated HBV DNA levels and development of HCC. Further studies confirmed this association, and the AASLD therefore recommended instituting HCC surveillance among patients with persistently elevated HBV DNA levels (>2,000 IU/mL).[1,13]

In summary, the updated AASLD guidelines recommend routine cancer surveillance among cirrhotic HBV carriers, noncirrhotic HBV carriers of Asian ethnicity (males over the age of 40 years and females over the age of 50 years), and Africans over the age of 20 years. HCC surveillance is also recommended among chronic HBV patients over the age of 40 years if they have persistent inflammatory activity on biopsy, elevated liver enzyme levels, and/or HBV DNA levels above 2,000 IU/mL.[1,13] In addition to factors associated with HBV, the AASLD guidelines also recommend initiating routine cancer surveillance for patients with any form of cirrhosis, including cirrhosis secondary to HCV (HCC risk of 3–8% per year), hemochromatosis (HCC risk >1.5% per year), and autoimmune hepatitis (HCC risk >1.1% per year).[1,20]

The available modalities for HCC screening include both serologic markers and radiographic tests. While alpha-fetoprotein (AFP) is the most commonly used serologic screening test for HCC, it has a sensitivity of only approximately 60% when standard cutoff recommendations are used.[21] Newer serologic markers, including descarboxyprothrombin (DCP) and heat shock protein 70, have not been adequately investigated as screening tools; in particular, the low sensitivity of DCP in early studies suggests it would not be suitable for use as a screening test.[22-26] Finally, recent studies have evaluated whether glycosylated AFP (AFP-L3) and/or the ratio of AFP-L3 to total AFP (AFP-L3%) could play a role in HCC diagnosis.[22,23,27-31] The use of AFP-L3% is not completely novel, as this marker has been widely and routinely used in Japan for HCC screening and outcome prediction after treatment. Several studies comparing AFP-L3% with total

AFP and other novel markers failed to demonstrate significantly improved sensitivity for HCC diagnosis. However, recent studies have demonstrated remarkably high specificities associated with AFP-L3%, suggesting that this ratio may be useful for improving risk stratification when used in combination with total AFP levels.[22,28-30] The largest risk for HCC appears to occur in patients with AFP-L3% levels above 10%.

In terms of radiologic screening tests, ultrasonography is most frequently used for HCC screening, but it has a sensitivity of 65–80%.[32] Some physicians have also considered quad-phase computed tomography (CT) scanning or magnetic resonance imaging (MRI) as alternative or complementary tools for screening, especially in patients with equivocal ultrasound examinations. However, widespread use of these technologies as primary screening tools has been limited by the high levels of radiation exposure associated with CT and the higher costs associated with both CT and MRI. Current AASLD guidelines recommend ultrasonography screening at 6-month intervals for patients at high risk of developing HCC.[1]

Staging Systems

Disease staging is particularly important in the management of HCC because it helps to predict prognosis and determine appropriate treatment options; the most effective staging systems incorporate information about both cancer stage and liver function. The Child-Turcotte-Pugh (CTP) model is primarily an assessment of liver function and is intended to predict prognosis and stratify disease severity to facilitate transplant allocation.[33] While still used as a complementary tool to help with treatment decisions or evaluate progression and/or regression of disease, the CTP model has largely been replaced by the Model for End-stage Liver Disease (MELD) score.[34,35] The MELD score is primarily used to assess disease severity for the purpose of defining a patient's listing status for liver transplantation. Higher MELD scores reflect more severe disease, poorer prognosis, and greater likelihood of liver transplantation, barring any absolute contraindications to transplantation.[36-39] While patients with HCC may be granted exception points that are added to their scores, the MELD system was not designed to assess HCC disease severity, and it does not provide good prognostic classification for these patients.

The 4 major HCC staging systems include the American Joint Committee on Cancer's tumor-node-metastasis (TNM) model, the Okuda classification model, the Cancer of the Liver Italian Program (CLIP) score, and the Barcelona Clinic Liver Cancer (BCLC) staging system. The TNM system has been criticized for its poor accuracy in assessing cancer stage, stemming mainly from its reliance on pathologic findings, and its incomplete reflection of liver function status. Its poor prognostic accuracy has limited its utility in the clinical management of HCC.[40-42] The Okuda classification model incorporates information about both tumor size and liver function. While this model has demonstrated accuracy in identifying end-stage disease, it is less consistent in stratifying early and intermediate stages of disease.[43] The CLIP score includes several components: CTP stage, tumor morphology, AFP level, and presence of portal vein thrombosis.

While comparative studies have demonstrated that CLIP scores are more accurate than the Okuda model for determining prognosis, the BCLC staging system has the greatest predictive power for survival rates.[44,45] Indeed, the BCLC staging system has emerged as the most accurate and comprehensive cancer model to show consistent prognostic determination. The BCLC model incorporates variables reflecting tumor stage, liver function status, and cancer-related symptoms (Figure 1).[46,47] The most significant advantage of the BCLC model over other staging systems is its ability to link BCLC disease stage to therapeutic options and then to provide estimates of survival outcomes for each treatment intervention based on comprehensive evaluation of prior published response rates. While future studies incorporating genomic and proteomic profiles of patients and their cancers will provide even more accurate prognostic data and more individualized therapy, the BCLC model is currently the most comprehensive and widely accepted staging system for HCC.

Surgical Approaches

Early detection and accurate staging of HCC are important because they determine surgeons' ability to offer appropriately aggressive therapy. Surgical approaches range from complete resection of small localized tumors to liver transplantation. Surgical resection has been shown to be most beneficial for solitary tumors in patients without cirrhosis, with postresection 5-year survival rates of 41–74% in this population.[48-54] Among patients with cirrhosis or multiple tumor foci, resection may not always be the most ideal treatment option. Liver function status, presence of portal hypertension, and evidence of decompensated disease are factors that should be carefully considered before resecting a tumor. While large tumor size is not an absolute contraindication to resection, the risk of vascular invasion and dissemination increases with tumor size; thus, a thorough evaluation is imperative to ensure that the lesion is well circumscribed.[55]

Another factor that affects the decision to pursue local resection is the risk of postresection tumor recurrence, as studies have reported postresection recurrence rates as
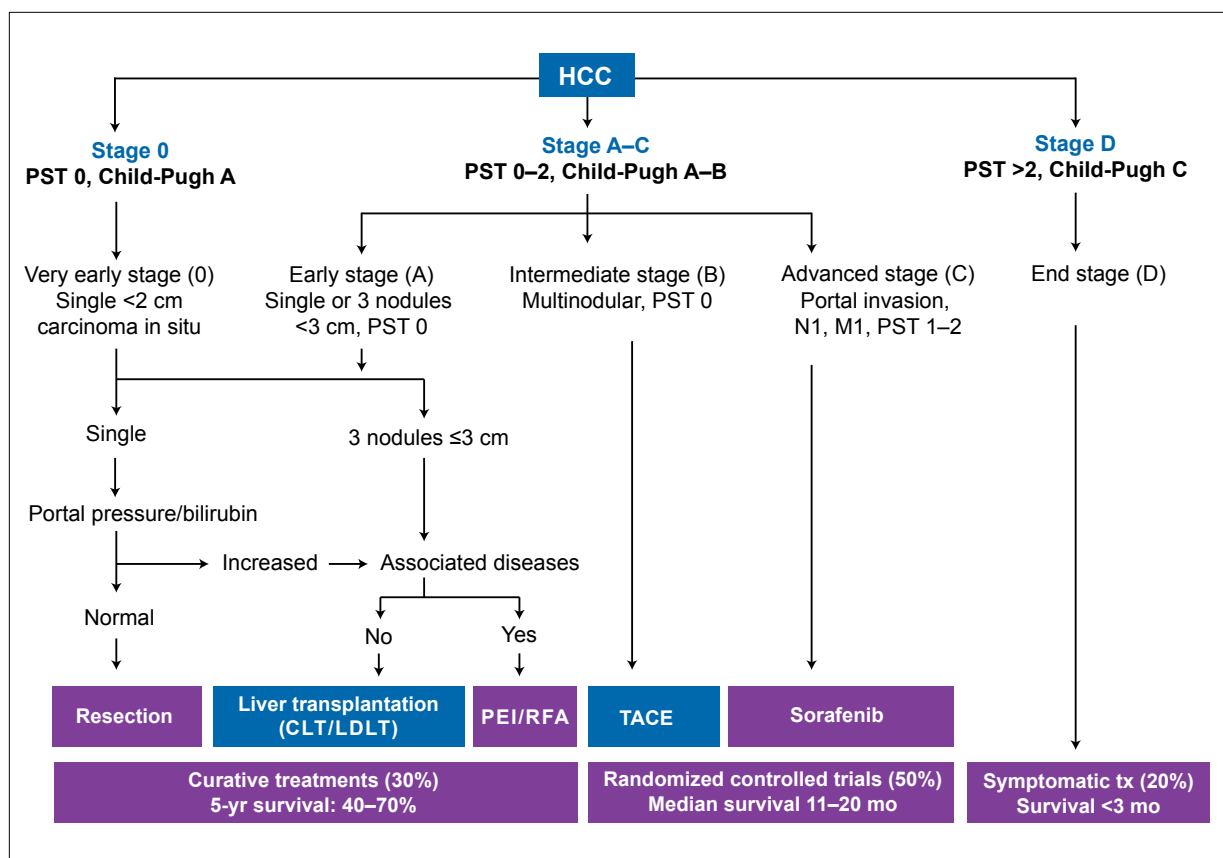
Figure 1. Barcelona Clinic Liver Cancer staging classification and treatment schedule. Patients with very early hepatocellular carcinoma (HCC; stage 0) are optimal candidates for resection. Patients with early HCC (stage A) are candidates for radical therapy (resection, liver transplantation, or local ablation via percutaneous ethanol injection [PEI] or radiofrequency ablation [RFA]). Patients with intermediate HCC (stage B) benefit from transarterial chemoembolization (TACE). Patients with advanced HCC, defined as the presence of macroscopic vascular invasion, extrahepatic spread, or cancer-related symptoms (Eastern Cooperative Oncology Group performance status 1 or 2; stage C), benefit from sorafenib. Patients with end-stage disease (stage D) will receive symptomatic treatment. Treatment strategy will transition between stages based on treatment failure or contraindications for procedures.

CLT=cadaveric liver transplantation; LDLT=living donor liver transplantation; M1=metastasis 1 stage; N1=node 1 stage; PST=performance status test; tx=treatment.

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high as 70% at 5 years. While de novo tumor development can occur following resection, the majority of HCC recurrences within 1–2 years are secondary to dissemination from the primary tumor. Preoperative evaluation must therefore consider recurrence risk via assessment of overall risk profile and tumor characteristics in order to offer appropriately targeted therapy for patients. While the best approach to postresection tumor recurrence has not been well studied, repeat resection is rarely ideal, as recurrences often have multifocal presentations reflecting their likely dissemination from the primary tumor. Instead, patients with a postresection recurrence may be

more suitable for salvage liver transplantation or other locoregional therapies, with or without oral multikinase inhibitors. Among patients with more advanced disease (multiple tumor foci or a possibility of metastasis) or patients with significant cirrhosis and impaired functional status, surgical resection is less beneficial and may actually contribute to the development of liver failure.

Among patients with unresectable disease, the most viable surgical option is often liver transplantation, frequently in conjunction with less invasive adjuvant therapy such as TACE or percutaneous ablation.[55-57] However, liver transplantation is not appropriate for all individuals,

and thorough evaluation is necessary to prudently allocate the scarce resources available. Due to the risk of post-transplantation recurrence of disease, HCC patients with extrahepatic disease or those with disease beyond currently accepted listing criteria are ineligible for transplantation. In an attempt to identify the most appropriate transplant patients, the Milan criteria, which consider both the number and size of tumor nodules, have emerged as the international standard by which potential transplant candidates are evaluated.[56] The Milan criteria—which state that patients are eligible for transplantation if they have a solitary tumor less than 5 cm or up to 3 tumors, each no more than 3 cm—have been validated in several studies. When surgeons adhere to these criteria, 5-year survival rates after transplantation range from 70% to 80%, and tumor recurrence rates are approximately 10%.[50,57-60]

Several studies have investigated the effect of expanding the Milan criteria, primarily by liberalizing the restrictions on tumor size. While some centers utilizing expanded criteria have reported promising results, with survival rates and recurrence-free rates similar to those obtained with strict adherence to the Milan criteria, national and international guidelines have not endorsed any expansion of current listing criteria.[61-66] Among these expanded criteria, the University of California San Francisco (UCSF) criteria (solitary lesion ≤6.5 cm or ≤3 lesions each ≤4.5 cm, with the total combined tumor diameter ≤8 cm) have been evaluated in several recent studies.[66,67] Since the initial report by Yao and colleagues that demonstrated acceptable survival rates using the UCSF criteria (90% 1-year survival rates and 75% 5-year survival rates), subsequent studies of expanded criteria have continued to demonstrate outcomes similar to those achieved with the Milan criteria.[66,67]

Recent interest has focused on utilizing a downstaging approach in which patients with HCC exceeding transplantation criteria are treated with locoregional therapy (ie, TACE and/or ablation therapy) in order to decrease the tumor burden to a point at which transplantation criteria are met.[68-70] One recently published experience with a downstaging protocol, by Yao and colleagues, included a large, prospective study cohort of 61 patients who were downstaged using TACE and/or RFA.[70] Early results from this ongoing, prospective study demonstrated promising survival outcomes, with post-transplantation survival rates among patients who received a transplant of 96.2% at 1 year and 92.1% at 4 years. While the success of these early studies has prompted some institutions to adopt both the UCSF criteria and the proposed downstaging protocols, other institutions have raised concerns about this approach. While decreasing tumor burden may allow patients who would otherwise be excluded from transplantation to be eligible for listing, some HCC

experts believe that large or multifocal tumors retain the same risk of recurrence despite successful downstaging. In addition, increasing the pool of potential transplant recipients may contribute to longer wait-list times, higher dropout rates, and greater wait-list mortality. With the ongoing and increasing scarcity of donor organs, many surgeons find it difficult to rationalize a liberalization of current listing criteria that would allow the inclusion of patients with more advanced disease and worse post-transplantation outcomes. However, advances in both surgical and adjuvant medical therapies are leading to significant improvements in post-transplantation mortality that will likely continue to push the upper threshold for liver transplantation.

Nonsurgical Invasive Therapies

Nonsurgical invasive therapies play an important role in treating HCC patients who are unsuitable for surgical resection or transplantation.[71] Percutaneous ablation techniques are safe and effective for primary treatment of small localized tumors or as a bridge to transplantation. Ablation techniques confer their therapeutic potential by destroying tumor cells, either by directly exposing tumor cells to toxic substances (eg, ethanol) or by modifying the temperature (eg, radiofrequency).

Percutaneous Ethanol Injection and Radiofrequency Ablation

The most common ablation modalities include percutaneous ethanol injection (PEI) and RFA.[71] Among patients with tumors less than 2 cm in size, PEI and RFA have similar efficacies, with both techniques achieving tumor necrosis in 90–100%.[72-75] However, RFA is often preferred over PEI, even in patients with smaller tumors, because RFA requires fewer treatment sessions and is more easily tolerated.[74,75] In patients with larger tumors, the efficacy of PEI declines significantly, with tumor necrosis rates of 70% for tumors 2–3 cm and 50% for tumors 3–5 cm.[72,73] RFA is more consistently effective than PEI for larger tumors, although RFA is still generally less effective in tumors over 3 cm. A recent meta-analysis evaluating the efficacies of PEI and RFA suggests that overall survival rates are better among patients treated with RFA than those treated with PEI.[74-78] Thus, while PEI has demonstrated similar rates of necrosis for smaller tumors, RFA continues to demonstrate the most predictable efficacy in both small and large tumors, and recent studies suggest that patients treated with RFA demonstrate superior survival outcomes.[76]

Given that RFA has shown promising outcomes, with some studies demonstrating 5-year survival rates of 70% among patients with tumors less than 2 cm,

recent studies have compared RFA with primary surgical resection. A small, prospective, randomized controlled trial comparing RFA with surgical resection recently demonstrated similar disease-free survival and overall survival rates between the 2 groups.[79] However, the study's relatively small sample size and its inclusion of patients with different stages of disease raise some questions about the impact of these results. If a significantly less invasive therapy such as RFA could consistently demonstrate outcomes similar to surgical resection, however, its role in the primary treatment of small localized HCC would need to be evaluated in greater detail. More studies are needed to confirm the promising outcomes achieved when RFA is used as the primary treatment modality, and more data comparing percutaneous ablation with surgical resection are needed before RFA can be considered as a potential first-line therapy for small localized HCC, except perhaps in patients who are not surgical candidates.

Microwave Ablation

Microwave ablation (MWA) is an emerging form of thermal ablation being evaluated for the treatment of HCC.[55,80-82] In a method similar to RFA, MWA utilizes electromagnetic waves with frequencies greater than 900 kHz to irradiate and ablate tumor foci. Although the benefits of MWA therapy are similar to those of RFA, MWA offers several theoretical advantages that need to be further studied. First, while the ablation provided by RFA is primarily passive, MWA utilizes active ablation heating. By virtue of its form of heat distribution, this latter method enables continuous and uniform ablation, which allows for the generation of higher temperatures and larger ablation zones, thus leading to higher rates of tumor necrosis. Second, MWA overcomes the "heat sink" effect, a common limitation of RFA that involves the cooling of blood flow in the immediate proximity of tumors, which can lead to incomplete ablation and reduced necrosis. While earlier studies comparing RFA and MWA demonstrated no statistically significant difference in efficacy, more recent studies using improved MWA modalities show promise. The clinical advantages of MWA over RFA and its potential to demonstrate greater rates of tumor necrosis with fewer treatment sessions need to be further investigated in head-to-head comparisons.

Transarterial Chemoembolization

Among patients with large multifocal HCC or those whose tumor characteristics are not appropriate for surgical or ablation therapy, TACE is recommended as a first-line, noncurative treatment for tumors without vascular invasion or extrahepatic spread.[83] TACE utilizes the neo-angiogenic properties of HCC, focusing its mechanism of action on the hepatic arterial supply from which the tumor receives its blood flow. The treatment process involves injection of intra-arterial chemotherapy—often suspended in lipiodol, a substance that is selectively retained within the tumor and increases chemotherapy exposure—to the affected hepatic lobe.[84-86] Following intra-arterial chemotherapy, the hepatic artery supply to the tumor is obstructed via angiographic catheter placement of one of several potential agents, which can include polyvinyl alcohol beads, starch microspheres, metallic coils, or autologous blood clots.[87-90]

Although this conventional form of TACE has been the most commonly utilized, the advent of embolic, drug-eluting microspheres offers a promising alternative that has nearly replaced conventional TACE at many institutions. While several studies have consistently demonstrated a clinical benefit from TACE, the significant side effects associated with the administered chemotherapy regimens have prevented the development of a clear consensus regarding the type of chemotherapy that should be used or the optimum frequency of treatment sessions.[71] With the introduction of embolic microspheres that are embedded with chemotherapeutic agents, however, treatment can be delivered in a controlled, sustained fashion to the tumor foci, which improves drug delivery and minimizes the effects of systemic chemotherapy exposure.[91-93]

In a recent multicenter, phase II, randomized clinical trial, doxorubicin-eluting beads demonstrated a trend toward higher treatment response rates and increased tumor necrosis compared to conventional TACE.[91] In addition, doxorubicin-eluting beads demonstrated better tolerability and safety. Doxorubicin-eluting beads were associated with significantly lower rates of serious liver toxicity and lower rates of chemotherapy-related side effects, both of which are major limitations of conventional TACE. While further studies are needed to confirm the improved safety profile of this method and to demonstrate similar or improved efficacy over the conventional procedure, TACE performed with drug-eluting beads will likely replace conventional TACE in the near future.[91-93]

Yttrium-90–labeled Microspheres

Finally, therapies utilizing more selective mechanisms or novel approaches for achieving local tumor necrosis have been emerging. Yttrium-90 (Y90)-labeled microspheres are administered in a procedure similar to that used for TACE, allowing for more specific, targeted therapy.[94-99] As with TACE, this procedure utilizes the hypervascularity of HCC, allowing the Y90 microspheres to be preferentially delivered to tumor foci, resulting in more directly targeted radiation. While administration of Y90 is contraindicated in patients with significant hepatopulmonary shunting, which could result in very high

levels of pulmonary radiation exposure, the relatively minimal embolic effects of Y90 allow it to be used safely in patients with portal vein thrombosis. Several studies evaluating this novel tool have demonstrated clinical safety as well as promising clinical efficacy.[94-99] A recent single-center, prospective, longitudinal cohort study of 291 patients treated with Y90 achieved response rates of 42–57%, which are similar to the rates of necrosis achieved with TACE.[97-99] While no randomized controlled trials have yet demonstrated the clinical benefit of Y90 compared to more established treatment modalities, early studies suggest that Y90 may be an additional treatment option for patients with HCC. However, this therapy needs to be further investigated in head-to-head comparisons with standard and accepted therapies.

Systemic Therapies

Available options for systemic treatment of unresectable HCC are limited, as studies investigating cytotoxic chemotherapy regimens have failed to demonstrate an impact on overall HCC survival rates.[100] However, newer agents that utilize antiangiogenic modalities have shown great potential. For example, sorafenib (Nexavar, Bayer) is a multikinase inhibitor that has been investigated in the treatment of advanced HCC. A large, randomized, placebo-controlled trial of 602 patients with advanced HCC that evaluated the efficacy of sorafenib was terminated early after interim analyses demonstrated a significant survival advantage associated with the treatment arm.[101] The study reported an overall decrease in the risk of death of 31%, with a median survival rate in the sorafenib group of 10.7 months compared to 7.9 months in the placebo group. The efficacy of sorafenib has been confirmed in subsequent studies, including a large, randomized, placebo-controlled trial in the Asia-Pacific region that included mostly HBV-related HCC.[102] Current guidelines from the AASLD recommend sorafenib as a first-line therapy in patients with unresectable HCC who are not appropriate candidates for percutaneous ablation or TACE but who maintain preserved liver function.[1]

Additional antiangiogenic agents are also being investigated. Bevacizumab (Avastin, Genentech), a human monoclonal antibody directed against vascular endothelial growth factor, and erlotinib (Tarceva, OSI), an epidermal growth factor receptor tyrosine kinase inhibitor, have demonstrated encouraging results in early studies, and further analysis of these agents is currently in progress.[103-105] While the development of these new agents, along with the recommendation of sorafenib, is currently targeted at advanced HCC, these novel agents may offer the most potential when used in conjunction with surgical resection and/or ablation therapies in an adjuvant or neoadjuvant fashion.[106] The combination of these agents with currently accepted, standard therapies in earlier-stage disease may offer not only prolonged survival but also, perhaps, a potential cure.

Conclusion

HCC remains one of the leading causes of cancer death worldwide. Advances in the understanding of HCC epidemiology and cancer biology have improved screening and surveillance programs, the primary goals of which are the early detection and treatment of HCC. Continued improvements in both surgical approaches and medical therapy for HCC have demonstrated significant benefits in overall survival rates. While liver transplantation remains a definitive therapy, the scarcity of available organs precludes this option for many patients with HCC. Novel systemic agents targeting the unique neoangiogenic properties of HCC have shown encouraging results; one such agent, sorafenib, is currently recommended for advanced HCC that is not amenable to standard therapies. The great potential of these novel agents lies in their possible role as an adjuvant or neoadjuvant therapy that could be combined with primary surgical resection or ablation. More studies are needed to investigate the possibility of such combination treatment approaches, but using these newer agents in earlier-stage disease offers the possibility of prolonging survival and may allow the development of a curative approach.

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