REVIEW ARTICLE

Current Updates in Diagnosis and Management of Hepatocellular Carcinoma with Special Reference to Interventional Radiology

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ABSTRACT

Hepatocellular Carcinoma (HCC) accounts for the sixth most common cancer, implying considerable disease burden. Liver Ultrasound (US) and the use of certain serum biomarkers, like Alpha-Feto Protein (AFP) and Protein induced by vitamin K absence or antagonist II (PIVKA-II) have gained popularity over time as screening methods for the detection of HCC. AFP is beneficial when used in combination with US or PIVKA-II to increase the validity of results and for smaller tumors (≤ 2 cm) to be detected.

The objective of this article is to recognize and address the growing role and potential of Interventional Radiology (IR) as a diagnostic and therapeutic field for the treatment of HCC. The use of contrast-enhanced CT or MRI has continued to gain popularity as a non-invasive yet accurate diagnostic tool. This paper also highlights the scope of newer treatment strategies adopted by Interventional Radiologists for HCC. Some key IR therapies include Radiofrequency Ablation (RFA), Transarterial Chemoembolization (TACE), and Transarterial Radioembolization (TARE) which are applied more efficiently due to the 2022 updated Barcelona Clinic Liver Cancer (BCLC) staging criteria that guide Interventional Radiologists to decide on a treatment strategy specific to the stage and each patient's unique medical history, enhancing patient care for liver cancer patients.

However, there is a need for more research in the field and for an internationally agreed consensus to set out guidelines regarding screening protocol for detection of HCC and predicting response to treatment.

Keywords: *HCC, interventional radiology, TACE, TARE, AFP, PIVKA-II, hepatocellular carcinoma.*

INTRODUCTION AND EPIDEMIOLOGY

Hepatocellular Carcinoma (HCC) ranks as the sixth most prevalent cancer and the fourth leading cause of cancer-related mortality, representing more than 80% of primary liver cancers globally [1]. The general trend observed is that the prevalence of HCC rises with age, hitting its peak at around the age of 70, as observed in Japan. However, contrary to the general trend, younger age of presentation of the disease has been observed in Chinese and black African populations. A notable male dominance has been observed, with males being twice as commonly affected as compared to females [2].

Resouce-limited nations contribute to 85% of HCC cases, of which Asia is estimated to carry >20 cases per 100,000 population [1]. Higher exposure to risk factors coupled with limited resources that subsequently lead to delayed detection and limitations in the usage of advanced treatment modalities for HCC contributes to the high disease burden in the region. This emphasizes the need for screening for HCC in high-risk populations since prognosis is highly dependent on tumor stage, which can range from curative options including surgery for tumor resection or transplantation if detected at an early stage, with an estimated 70% 5-year survival rates to palliative therapies available for advanced stages, with a median survival of 1-2 years [3].

Predisposing conditions for HCC include chronic Hepatitis B and Hepatitis C infections, alcohol, obesity, diabetes, Nonalcoholic Fatty Liver Disease (NAFLD), and toxins like aflatoxin and aristolochic acid. Whereas, studies have proven that coffee, statins, metformin, and aspirin serve as protective factors, preventing the onset and progression of HCC [1].

Both alcohol consumption and NAFLD eventually lead to cirrhosis which causes HCC, especially if other risk factors like diabetes are present. Chronic Hepatitis B (HBV) infection plays a synergistic effect with Aflatoxin on the occurrence risk of HCC. Aflatoxin B1 (AFB1) which is specifically found in areas of the world with warm, humid conditions is a powerful carcinogen that contributes to the development of HCC, so vaccinating against HBV is recommended in areas where both HBV and Aflatoxin coexist to lower the risk.

Ultrasonography and Serum Biomarkers as Surveillance and Diagnostic Markers

As the incidence of liver cancer keeps rising, HCC surveillance is recommended in all high-risk populations, which includes those with chronic HBV infection who have a higher risk for developing HCC, including those identified through risk assessments like the CU-HCC or PAGE-B scores. This also includes

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individuals with Child-Pugh Class A or B cirrhosis of any origin, as well as those with Child-Pugh Class C cirrhosis who are awaiting liver transplantation. Additionally, chronic hepatitis C patients with advanced fibrosis are also categorized as being at an increased risk for disease development [4].

According to a recent study, almost half the patients had HCC identified through screening which resulted in better disease outcomes in terms of diagnosis, management, and overall survival [5]. The American Association for the Study of Liver Diseases (AASLD) and the Asia Pacific Association for the Study of the Liver recommend 6-monthly Liver ultrasonography (US) coupled with serum Alpha-Feto protein (AFP) for HCC surveillance. Santi *et al.* further emphasized that semiannual surveillance leads to the detection of tumors at an earlier stage before tumor progression into advanced stages as compared to annual screening, which subsequently leads to the availability of more effective treatments [6]. Further studies also prove that semi-annual screening has equal efficacy to 3 or 4-month intervals [7].

To increase the reliability and validity of results, imaging is often combined with serum AFP levels as a biomarker for HCC. Chang *et al.* conducted a study in which the cut-off value for AFP was assumed to be 20 ng/ml; it showed that when AFP alone was used for HCC detection, the sensitivity and specificity were 52.9% and 93.3%, respectively whereas the US alone had sensitivity and specificity of 92.0% and 74.2%, respectively. However, a combination of US and AFP showed a sensitivity and specificity of 99.2% and 68.3%, respectively [8]. Hakeem *et al.* conducted a study in which a literature search of 13 studies (12,159 patients) was done which showed that an AFP level exceeding 1000 ng/mL is associated with less favorable results after liver transplantation [9].

With the growing prominence of systemic therapies for the treatment of HCC, the significance of serum AFP in assessing response to treatment is starting to gain just as much significance as conventional imaging techniques, which are largely dependent on tumor size and vascularity [10].

Although, conventionally AFP has been a key biomarker in the diagnosis and assessment of HCC due to its limited specificity and sensitivity especially with small tumor size, as proven by a study conducted by Tarao *et al.,* in which 933 patients were further divided based on tumor size into two groups, one with 394 patients and tumor size of less than 2 cm and other having 539 patients and tumor size > 2 cm and the results showed that half of the individuals with smaller tumor size had AFP values in the normal range [11], hence limiting the reliability of using solely AFP for diagnosis, especially in small tumor size.

For this reason, Protein induced by vitamin K absence II or antagonist II (PIVKA-II) is another biomarker that has widely gained popularity when used in combination with AFP. In Tarao's study, when patients with nodules ≤ 2 cm were compared with those with larger size, there was a significant difference observed in the positive ratio of PIVKA-II ($P < 0.0001$) but there was no significant difference in AFP ($P = 0.4254$) [11].

A cohort conducted in 2023, involving 260 high-risk for HCC patients of whom 219 patients were diagnosed with HCC, confirmed by biopsy in seven patients while others got their diagnosis by imaging. PIVKA-II had higher significance for HCC diagnosis as compared with AFP, hence it can even be used without AFP for HCC surveillance and diagnosis [12, 13].

Despite their significance, AFP and PIVKA-II, when used in isolation, each have their own limitations in the diagnosis of HCC and predicting response to treatment. For this purpose, Piratvisuth *et al.* studied the novel GAAD algorithm which produces a semi-quantitative result using a combination of PIVKA-II, AFP values, patient's age, and gender. Results showed a sensitivity of 71.8% and a specificity of 90.0% for early-stage disease recognition [14]. However, serial serum biomarkers and the US can be an expensive screening tool for patients in low-middle income countries where global occurrence of HCC is most prevalent, hence restricting the practicality of using these in a resource-limited setting.

Differential Diagnosis of Raised AFP and PIVKA-II

AFP can also be elevated in conditions other than HCC, some of which include benign conditions like hepatitis, normal pregnancy, cirrhosis, ataxia telangiectasia, hereditary tyrosinemia, and inflammatory bowel disease or nonseminomatous germ cell tumors. Patil *et al.* studied the case of a 35-year-old with chronic hepatitis B for the past 12 months and non-compliant with medications, presenting with jaundice for the past seven days. He did not have any evidence of HCC but had high AFP levels (740.9 ng/ml) which decreased with the continuation of antiviral therapy [15].

Although the significance and acceptance of PIVKA II continue to grow as a marker for HCC, research also shows that there are multiple factors other than HCC that can result in an elevated PIVKA II, which limits the specificity of the biomarker. Some of these factors

include primary gastric adenocarcinoma, vitamin K deficiency, Alcoholic Liver Disease (ALD), underlying renal failure, graft rejection after liver transplantation, the administration of antibiotics that alter gut flora, inflammatory bowel disease and the administration of warfarin [16]. Kudo *et al.* studied a patient with type IIc gastric cancer; the patient had both elevated AFP and PIVKA II, 2810 ng/ml and 2.45 AU/ml respectively. US, CT scan, MRI, radiocolloid liver scan, and angiography were all used to confirm the absence of a co-existing hepatic tumor. In the gastric tumor, cells with hepatoid differentiation were found that could explain the elevated AFP and PIVKA II levels [17].

Lee *et al.* studied the effect of warfarin on PIVKA II, where 149 outpatients were studied to prove that PIVKA-II levels significantly increased post-initiation of warfarin therapy [18]. Another study also further supports this stance that the level of PIVKA II in warfarin dependent individuals is higher than control groups even if the protein production in the liver is the same for both groups [19].

Role of Interventional Radiology (IR) in Treatment and Diagnosis of HCC

Interventional Radiology (IR) is an evolving discipline with a crucial function in disease identification and treatment, using advanced yet minimally invasive and widely proven and accepted strategies. IR has gained significant popularity over the years as radiological imaging and targeted logo regional therapies are integral for the management of HCC patients to avoid systemic side effects and invasive procedures which are increasingly becoming obsolete.

Diagnosis

Ultrasound has been used for decades for HCC diagnosis and surveillance, however, if surveillance US shows nodules of 1cm or greater, contrast-enhanced CT or MRI is suggested for disease evaluation. In contrast enhanced CT or MRI, arterial enhancement stronger than the surrounding liver (wash-in), and hyposignal intensity compared to the surrounding liver (wash-out) in the venous phase is observed which portrays the vascular derangements occurring during hepatocarcinogenesis. This has a sensitivity of around 60% with a 96-100% specificity [20, 21].

In 2020, Van Wetter *et al.* [22] studied Hepatobiliary phase (HBP) images to distinguish between benign and malignant liver lesions, specifically in patients with Budd-Chiari syndrome (BCS). Most benign lesions showed homogeneous or peripheral hyperintensity on HBP images while all HCCs were homogeneously hypointense, thus HBP images hold great significance in differentiating between benign lesions and HCC [22].

With the use of hepatobiliary contrast for liver MRI with the inclusion of diffusion-weighted sequences along with radiotracers for positron-emission tomography (PET) in recent years, radiological diagnosis for HCC has gained even more popularity. After analyzing a large number of patients, several studies have proved the superiority of using contrast-enhanced MRI, specifically gadoxetate disodium as a contrast agent over a CT scan for the identification of hypervascular HCC [23, 24].

Treatment Strategies

Imaging is used for not only detecting the extent of tumor involvement, and the stage of disease but also for treatment allocation based on the stage, subsequently predicting the prognosis of the disease. The treatment strategies can range from Radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) for early and intermediate stages of HCC, respectively. Other IR techniques like imaging-guided brachytherapy, and transarterial radioembolization (TARE) can also be helpful in treating HCC [24]. Transarterial chemoembolization involves injecting a chemotherapeutic and an embolic agent into the hepatic artery whereas radioembolization consists of injecting Yttrium 90 loaded microparticles into the hepatic artery [25].

In 2022, the Barcelona Clinic Liver Cancer (BCLC) staging released an updated criteria that stratifies patients with HCC, which involves a complex system for the allocation of liver lesions to a certain BCLC stage, subsequently guiding treatment strategies specific to the stage [26]. While the BCLC model guides treatment options for each stage, it also focuses on the need for an individualized treatment strategy for each patient which will be based on the clinical judgment and personal expertise of the radiologist, Interventional Radiologist, Interventional Oncologist, and surgeon involved in the care of the patient. This personalized treatment strategy means that in certain cases, keeping in mind the patient's personal medical record and socio-economic factors, there may be a step-up from the usual recommended treatment strategy for that specific stage or even to no treatment *i.e.* the Treatment Stage Migration (TSM) concept [27]. This transformed the rigid BCLC system introduced in 1999 into a more flexible and adaptable system, designed to cater to the needs of every HCC patient individually which called for Interventional Radiologists to take a central role in the management of HCC.

BCLC-0 involves a liver nodule ≤2 cm without vascular invasion or extrahepatic spread. As part of BCLC-0 management, the possibility of Liver Transplantation (LT) must be the initial consideration [28]. If LT is an option, specifically for patients within the Milan criteria resection must be initially considered. However, if due to certain individual factors of the patient LT is not a suitable option, the disease prognosis with image-guided ablation (through radiofrequency (RF), microwave (MW), or percutaneous ethanol injection in some cases) is similar to resection [29, 30]. Both RFA and MWA operate on the principle of thermal ablation for killing tumor cells while sparing maximal healthy liver tissue. In RFA, a needle that delivers high-frequency electric current is used as the heat-generating source to maximize cell death by the high temperature generated. RFA is a minimally invasive procedure that can be safely repeated several times, its cost-effectiveness, efficacy, and limited systemic side effects on the body make it a suitable choice in many cases. However, not only is the procedure painful but the risk of injury to surrounding structures like the lungs and biliary tree makes it a risky procedure. The tumor margins may also remain positive after the procedure because of the heat-sink effect which brings into question the practicality of using this approach in HCC patients.

In Microwave ablation (MWA), heat produced using high frequencies is used to alter the polarity of water molecules within tissues. In MWA less time is needed to create an ablation zone than in RFA. The heat sink effect is also lesser in MWA, making it more effective for perivascular tumors. MWA can also be associated with complications like ascites, pleural effusion, liver abscess, and perforation of nearby organs.

BCLC A is defined as a solitary nodule irrespective of size or as a multifocal HCC with up to 3 nodules (none of them >3 cm). In BCLC A, resection is preferred in nodules exceeding 2 centimeters. In patients where LT is not possible having multifocal tumors, ablation is recommended rather than resection for HCCs ≤ 3 cm and TACE otherwise [31].

BCLC B or the intermediate stages is further subdivided into three categories as per the tumor burden but without any specific cut-off values for each subdivision. The first subgroup includes patients who meet the 'Extended Liver Transplant criteria'. Patients in the second group have preserved portal flow and well-defined nodules; patients in this group are potential candidates for TACE. The third group comprises patients with infiltrative disease with extensive bilobar liver involvement.

TACE involves a combination of embolization and delivery of a cytotoxic medication which is a mix of iodinated poppy seed oil along with anticancer agents like cisplatin, doxorubicin, carboplatin, epirubicin, mitoxantrone, and mitomycin C12 injected through a trans arterial route to the vascular supply of the tumor. Along with downsizing and shrinking the tumor size, TACE has the added advantage of delivering a higher magnitude of drug concentrations to tumor cells and staying in the target tumor cells for a longer duration, hence proving to be more toxic for tumor cells while limiting systemic toxicity which is otherwise associated with systemic chemotherapy as most of the drug is concentrated in and limited to the tumor cells, not even damaging the normal liver cells. However, TACE can not be used when there is main portal vein thrombosis, distant metastasis, or glomerular filtration rate of less than 40 mL/min/1.73 m^2. Vomiting, renal failure, cardiac toxicity, bone marrow aplasia, hepatic abscess or cholecystitis, and post-embolization syndrome are some of the side effects associated with TACE.

In patients with portal vein thrombosis where TACE is contraindicated, TARE can be safely used. TARE combines hepatic artery cannulation with radiotherapy by delivering a high radiation dose to tumor cells within the liver. Radiation used in TARE may damage surrounding organs which were primarily not damaged by HCC itself. Cholecystitis, pneumonitis, and gastric and esophageal ulcers develop because of these radiations. GI symptoms, lethargy, mildly elevated body temperature, and lymphopenia are some side effects associated with TARE [32].

However, in actual clinical settings, TACE or TARE needs the expertise of Interventional Radiologists and instruments that might not always be available in low-middle-income countries. Grégory *et al.* carried out a cross-sectional study among French Interventional Radiology centers. 39% of the 44 centers that responded performed TRA for TACE and/or TARE, with the patient's well-being after the procedure being the chief consideration. A lack of technical experience was the reason reported by 33% of the centers not performing TRA, however, all 27 showed plans to adopt TRA within two years [33].

Brown *et al.* analyzed 2465 patients for comparison of TACE *versus* TARE which showed that TARE had a longer time to progression (TTP) than TACE, however, no difference was found in overall survival (OS) between the two treatment modalities for HCC [34]. The longer TTP in TARE may be attributed to a failure in the detection of tumor progression as radiation therapy may

lead to inadequacy in the radiographic interpretation of the tumor meanwhile no difference in overall survival may be because of bias due to many factors, including the discrepancies in follow-up care post-TACE or TARE in the patients or because of different treatment regimen for each patient both before and after receiving TARE or TACE therapy.

Systemic therapy is recommended for BCLC C or advanced-stage HCC [35]. The use of Atezolizumab alongside Bevacizumab (Atezo-Bev) results in improved outcomes over sorafenib [36, 37]. BCLC stage D encompasses individuals with significant tumor-associated complaints, having a prognosis of around 3 months for which palliative care and symptomatic management are recommended.

CONCLUSION

As the morbidity and mortality of HCC keep rising, it calls for advancements in research and technology which will subsequently lead to earlier detection and more advanced and focused treatment options with less systemic side effects which is why Interventional Radiology has emerged as a major discipline in recent times for the management of HCC. For diagnostic purposes, the use of serum biomarkers like AFP and PIVKA-II has held significance for some time but now the use of imaging modalities like Ultrasound, contrast-enhanced CT or MRI has also started gaining popularity as an effective and readily available diagnostic tool for accurate detection of small tumors and tumor recurrence post-treatment.

The role of image-guided therapies has become routine for the treatment of HCC as a pragmatic therapy plan due to reduced mortality, lower tumor recurrence rates, cost-effectiveness, and faster post-procedural recovery times when compared to elaborate surgical techniques or Liver Transplantation. These improved patient outcomes and practicality of the strategies mean that these therapies can be widely used in a resource-limited setting in low-middle income countries, provided that they are performed precisely and diligently under the care of an interventional radiologist holding great expertise in the field.

The role of interventional radiology will continue to grow in the coming years as with the updated 2022 BCLC staging criteria, the focus has shifted from rigid guidelines for each HCC stage to a more patient-centered holistic approach in treatment, optimizing outcomes for liver cancer patients. Interventional Radiologists should continue working alongside oncologists, hepatologists, and surgeons in the future to come up with more focused and successful intervention strategies to enhance patients' quality of life and ensure better prognosis of disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

Azeemuddin M- Conceptualization, manuscript drafting and review

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Iqbal J- Manuscript review and editing

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