

# Egyptian Society of Liver Cancer Recommendation Guidelines for the Management of Hepatocellular Carcinoma

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**Abstract:** Globally, hepatocellular carcinoma (HCC) is the fourth most common cause of death from cancer. The prevalence of this pathology, which has been on the rise in the last 30 years, has been predicted to continue increasing. HCC is the most common cause of cancer-related morbidity and mortality in Egypt and is also the most common cancer in males. Chronic liver diseases, including chronic hepatitis C, which is a primary health concern in Egypt, are considered major risk factors for HCC. However, HCC surveillance is recommended for patients with chronic hepatitis B virus (HBV) and liver cirrhosis; those above 40 with HBV but without cirrhosis; individuals with hepatitis D co-infection or a family history of HCC; and Nonalcoholic fatty liver disease (NAFLD) patients exhibiting significant fibrosis or cirrhosis. Several international guidelines aid physicians in the management of HCC. However, the availability and cost of diagnostic modalities and treatment options vary from one country to another. Therefore, the current guidelines aim to standardize the management of HCC in Egypt. The recommendations presented in this report represent the current management strategy at HCC treatment centers in Egypt. Recommendations were developed by an expert panel consisting of hepatologists, oncologists, gastroenterologists, surgeons, pathologists, and radiologists working under the umbrella of the Egyptian Society of Liver Cancer. The recommendations, which are based on the currently available local diagnostic aids and treatments in the country, include recommendations for future prospects.

**Keywords:** hepatocellular carcinoma, clinical recommendations, Egyptian society of liver cancer, hepatitis c virus, Egypt, guidelines

## Introduction

Globally, the prevalence of hepatocellular carcinoma (HCC), which is the fourth most common cause of cancer-related death, has been increasing over the last 30 years.<sup>1</sup> In 2018, the number of deaths caused by HCC worldwide was reported to be 781,631, which is higher than the 746,000 deaths reported in 2012.<sup>2</sup> Furthermore, in 2020, HCC was reported to be the most common cancer type in Egypt and the leading cause of mortality among all cancers, causing more than 26,000 deaths.<sup>3</sup> The incidence of HCC is on the rise due to the increase in the number of screening programs and the prolonged survival rate of patients with liver cirrhosis and nonalcoholic steatohepatitis (NASH).<sup>4</sup> Chronic liver diseases, which are a primary health concern in Egypt, are associated with high economic costs, a high disease burden, and poor prognoses, including HCC development.<sup>1</sup> In 2008, the estimated seroprevalence of the hepatitis C virus (HCV) in people aged 15–59 years was 14.7%, and this value was reduced to approximately 10% in 2015.<sup>5,6</sup> In 2019, the estimated HCV seroprevalence dropped to 4.6% among people aged above 18 years.<sup>1</sup> This significant decrease in the seroprevalence of HCV resulted from the immense efforts of the Egyptian government in screening almost 60 million Egyptians and treating more than 2 million patients infected with the virus. In 2020, the “100 Million Healthy Lives” campaign attained its objectives, making Egypt the first country in the world to reach the World Health Organization (WHO) HCV elimination target of reducing the HCV-related mortality rate by 65% and the incidence of the infection by 90%.<sup>7</sup> This success story is believed to be an essential strategy in decreasing the incidence of HCC in Egypt as a secondary preventive approach.<sup>7</sup>

Regarding hepatitis B virus (HBV), A meta-analysis spanning from 1983 to 2002, which incorporated 13 Egyptian studies, suggested a 6.7% HBV prevalence in healthy individuals and 25.9% among those with HCC.<sup>8</sup> The 2015 Egyptian Health Issues Survey (EHIS) demonstrated that the estimated prevalence of HBV was 1% based on HBsAg seroprevalence from a sample of 26,047 healthy individuals aged 1–59 years and 1.56% in a subgroup of 16,003 participants aged 15–59 years.<sup>9</sup> The most recent meta-analysis reported a consolidated national prevalence of 3.67%. Notably, children below 20 years, who were vaccinated against HBV in their infancy, exhibited the lowest prevalence at 0.69%. Specific groups showed varied prevalence: pregnant women at 2.95%, blood donors at 1.8%, and healthcare workers at 1.1%. Furthermore, when assessing gender differences, HBV prevalence was higher in males (3.75%) compared to females (2.2%). Overall, the trend indicates a decreasing prevalence of HBV in Egypt over the years.<sup>10</sup>

In 2015, an observational study involving 154 physicians from Egypt reported that 93% of physicians aged >45 years and 75% of physicians aged <45 years depended on guidelines when managing patients with HCC.<sup>11</sup> The study also demonstrated that 71% of physicians in the Ministry of Health (MOH) were not aware of the existence of any guidelines (local or international) due to a lack of awareness or limited interest, as per the authors.<sup>11,12</sup> The current diagnosis and treatment of HCC in the country are in line with the existing international guidelines such as those of the European Association for the Study of Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the Japan Society of Hepatology (JSH). However, the treatment options, in terms of availability, cost, and variation of the patient population, are limited in Egypt. There is also a paucity of available data on HCC in Egypt compared to other countries available worldwide, the high prevalence of the disease notwithstanding.

This document aims to provide recommendations to standardize the management of patients with HCC in Egypt based on the currently available evidence. The recommendations are developed under the umbrella of the Egyptian Society of Liver Cancer (ESLC). The guidelines define the use of surveillance, diagnosis, and therapeutic strategies recommended for these patients. Users of these guidelines should be aware that the recommendations are intended to guide clinical practice in situations where all the required resources and therapies are available.

## Methodology

The guidelines development team consisted of a group of Egyptian experts in different specialties working in the field of HCC, including 16 hepatologists, 12 Oncologists, 8 interventional radiologists, one pathologist, and 4 liver and transplant surgeons from 11 different centers. All panelists have more than 20 years of experience in HCC management in their relevant fields. Experts with different HCC management experience levels were selected equally to minimize the bias toward interventional-dominated opinions. Each panelist is either an active board member of an academic society working in HCC, a member of the HCC multidisciplinary team in a recognized institution, someone who contributed

to guidelines development on this subject, or someone who published scientific manuscripts on HCC management. Even though all panelists are of academic background, they fairly represent Egypt's governmental and private healthcare sectors. The panel identified, prioritized, and selected relevant topics on which a comprehensive literature search was performed. A literature search was conducted on Medline via PubMed from January 2015 to October 2021 to collect relevant information. The following search terms were used in combinations: ((carcinoma, hepatocellular [MeSH Terms]) OR (liver neoplasms [MeSH Terms])) AND ((population surveillance [MeSH Terms]) OR (diagnosis [MeSH Terms]) OR (neoplasm staging [MeSH Terms])) AND (disease management [MeSH Terms]) AND ((Egypt [MeSH Terms]) AND ((guideline [MeSH Terms]) OR (practice guideline [MeSH Terms])). Initially, the titles and abstracts of the retrieved records were screened, followed by full texts of the publications that addressed the guideline objectives. A manual search of the references of retrieved publications was also conducted. Besides, the last version of HCC management guidelines of major international societies, including the AASLD, EASL, JSH, and Asia Pacific Association for the Study of Liver (APASL), were referred to for additional statements.

The clinical practice guidelines methodology was used to agree on the recommendations. All experts voted on the recommendations in two consensus meetings held in December 2021. The level of evidence (LOE) of the retrieved statements was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Table 1).<sup>13</sup> The statements were primarily extracted from studies with high-quality evidence. Additional statements were retrieved from studies with lower-quality evidence whenever deemed necessary by the committee. Forty-one statements were developed, clustered, and distributed according to the defined working groups, including surveillance and epidemiology, diagnosis and risk assessment, early and advanced disease management, and follow-up. Statements with a voting percentage of 75% or more were considered "consensus reached", which was observed to be 95% (39/41). Additionally, areas of future research were identified to guide future prospective clinical trials. All the consented recommendations are presented in Table 2.

## Discussion

### Screening and Surveillance for HCC

#### Significance of HCC Surveillance in Egypt

##### Consensus Statements

The panel unanimously agreed (100%) on the need to adopt highly-sensitive, affordable, and accessible screening tools to identify populations predisposed to HCC in Egypt. The experts highlighted the change in HCC epidemiology worldwide and emphasized the significance of HCC screening and the selection of the right patients for screening. A meta-analysis and several local studies support the need for surveillance, proving that HCC surveillance is associated with a better prognosis and significant improvement in early tumor detection, receipt of curative therapies, and overall survival.<sup>9,11</sup> Early diagnosis can provide curative treatment options such as transplantation, surgical resection, and percutaneous ablation, which are not possible if the disease is detected at an advanced stage.<sup>14,15</sup> HCC surveillance with either AFP and US or multiphasic multidetector CT is economical, with a cost-effectiveness ratio of less than 50,000 USD quality-adjusted life year compared to no surveillance.<sup>15</sup> Accordingly, all panel experts (100%) agreed that HCC surveillance is cost-effective and associated with improved early-stage detection, high curative treatment rates, and prolonged survival.

**Table 1** Quality of Evidence and Definitions

High quality—Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate quality—Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
Low quality—Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low quality—Any estimate of the effect is very uncertain.

**Table 2** Consensus on HCC Management in Egypt

Sr.No	Recommendation	Voting Percentage	Level of Evidence
1	There is a need to adopt highly-sensitive, affordable, and accessible screening tools for the identification of at-risk populations for HCC in Egypt.	100%	High
2	Adequate surveillance for HCC is associated with improved early-stage detection, curative treatment rates, and prolonged survival. HCC surveillance has also been shown to be cost-effective.	100%	High
3	Patients with chronic hepatitis C (HCV) infection, especially those with associated cirrhosis, are associated with the greatest risk of HCC in Egypt, owing to its high prevalence in the Egyptian population.	100%	High
4	HCC surveillance is recommended in patients with cirrhosis, even after the eradication of HCV with DAA therapy.	96.6%	High
5	All patients with chronic hepatitis B virus (HBV) infection and cirrhosis require HCC surveillance. Patients with HBV without cirrhosis require HCC surveillance if they are: <ul style="list-style-type: none"> <li>– Aged &gt;40 years old</li> <li>– Having associated hepatitis D co-infection</li> <li>– Having a family history of HCC.</li> </ul>	100%	High
6	HCC surveillance is recommended in patients with nonalcoholic fatty liver disease (NAFLD) with significant fibrosis or cirrhosis (F3 or F4).	100%	Moderate
7	All patients with cirrhosis due to secondary etiologies require HCC surveillance, including hereditary hemochromatosis (HH), primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), and alpha 1-antitrypsin deficiency (A1AT).	100%	High
8	Ultrasound (US) is the modality of choice for regular HCC surveillance due to its availability and affordability, despite its limited reliability in patients with truncal obesity or marked parenchymal heterogeneity. Surveillance using a combination of US and alpha-fetoprotein (AFP) monitoring is recommended every four months to be performed by a qualified physician.	91.7%	High
9	A protein induced by Vitamin K Absence-II (PIVKA-II) and AFP-L3 can be considered in conjunction with US every four months according to availability and affordability.	90%	High
10	The inclusion of biomarkers, such as PIVKA-II and AFP-L3, in conjunction with US in the follow-up of HCC after treatment is recommended.	100%	low
11	The adoption of screening scores such as the GAAD (Gender, Age, AFP, DCP) and GALAD (Gender, Age, AFP, DCP, AFP-L3) scores is encouraged.	75%	Low
12	In at-risk patients, the recognition of a nodule measuring >10 mm on US should be followed by multiphase CT or contrast-enhanced MRI with diffusion. The choice of one modality over the other should be individualized.	100%	Low
13	Multiphase CT and MRI exams could be performed, interpreted, and reported through the CT/MRI Liver Imaging Reporting and Data System (CT/MRI LI-RADS).	95.24%	Low
14	Single imaging techniques (CT or MRI) are recommended to confirm the typical vascular pattern for lesions measuring 10–20 mm.	100%	Moderate
15	Liver nodules measuring <1 cm or 1–2 cm [LI-RADS 1 or 2] should be followed by US after three months. *	100%	moderate

(Continued)

Table 2 (Continued).

Sr.No	Recommendation	Voting Percentage	Level of Evidence
16	For indeterminate lesions (devoid of characteristic imaging patterns of HCC) LI-RADS-3, the following options can be used without any specific preference: <ul style="list-style-type: none"> <li>– Follow-up imaging if the lesion measures less than 2 cm</li> <li>– Imaging with an alternative modality of alternative contrast agent</li> <li>– Biopsy</li> </ul>	88.24%	Low
18	The Barcelona Clinic Liver Cancer (BCLC) staging system is the recommended system as it offers the most prognostic information, including an assessment of the tumor burden, liver function, and patient survival.	88.24%	High
19	The international classification trends are preferred to subclassify the Intermediate Stage BCLC-B into 3 or 4 subgroups according to the liver status, the number of lesions, and the type of lesions (infiltrative).	100%	Low
20	The adoption of the ALBI score, in addition to the Child-Pugh score and the MELD score, is recommended for the assessment of the liver status before HCC treatment.	95%	Moderate
21	Endoscopic assessment of any HCC patient: Upper GIT endoscopy is advised before receiving systemic therapy or surgery.	75%	Low
22	A multidisciplinary team (MDT) including the following is recommended for HCC management: Hepatologists, surgeons, interventional radiologists, clinical oncologists, clinical pharmacists, pathologists, nutritionists, radiologists, and transplant surgeons.	100%	Moderate
23	Hepatectomy is indicated, with a well-established efficacy and survival benefit, in Child-Pugh Class A liver function without clinically significant portal hypertension (CSPH) integrated with the ALBI and/or p-ALBI.	94.44%	Moderate
24	Unresectable lesions measuring up to 4 cm are subject to local ablative therapy by radiofrequency ablation (RFA) or microwave ablation.	88%	Low
25	Transarterial chemoembolization (TACE) is mainly indicated in hypervascular HCCs classified as BCLC-B, well-defined non-infiltrative HCC lesions, and a Tumor burden of less than 50% of the total liver volume.	88.89%	Moderate
26	Single lesions (4–6 cm) that are beyond local ablative therapy and are ineligible for surgical resection and transplantation could benefit from a combination of heat ablation and chemoembolization.	95.24%	Low
27	Scoring for intermediate HCC before TACE, such as the HAP score, the STATE score, and the ART-score post-TACE, are acceptable	100%	Low
28	Transarterial radioembolization (TARE) is an option in patients with: <ul style="list-style-type: none"> <li>– Large tumor burden with tumors measuring &lt;8.5 cm</li> <li>– Segmental or partial portal vein thrombosis.</li> </ul>	100%	Low
29	As the liver transplantation program in Egypt is a living donor program, more expansion in the transplantation criteria using different staging systems such as the UCSF and “Up-to-7” criteria can be applied.	100%	Low
30	The recommended interval to monitor tumor behavior after downstaging and before liver transplantation is within at least six months.	100%	Low
31	The cut-off level of AFP before liver transplantation is <1000 ng/mL.	100%	Low
32	Patients with ART scores of >1.5 after the first TACE or two consecutive imaging findings of non-response or evidence of decompensation should be considered for next-stage migration to systemic therapy.	100%	Moderate

(Continued)

**Table 2** (Continued).

Sr.No	Recommendation	Voting Percentage	Level of Evidence
33	The following sequence of systemic therapy is recommended: First line: atezolizumab/bevacizumab Alternative first line: sorafenib or lenvatinib Second line: After immunotherapy or TKI [regorafenib, cabozantinib, ramucirumab].	100%	Moderate
34	Adjuvant systemic treatment is still not recommended in clinical practice, and further studies are needed to approve this recommendation.	100%	Low
35	In certain circumstances, such as the presence of evidence of microvascular invasion in a resected liver with HCC, systemic treatment may be recommended as an adjuvant treatment.	92.86%	Low
36	Using the mRECIST Criteria in the assessment of progression and radiological response after HCC management is recommended.	100%	Low
37	The optimum timing of progression assessment after immunotherapy is four cycles, which is equivalent to 12 weeks.	100%	Low
38	External beam radiotherapy could be accepted in HCC patients under special indications.	100%	Low
39	Prospective concepts of combined HCC therapy, such as TACE and then systemic therapy (TKIs or immunotherapy), could be accepted.	100%	Low
40	Patients with BCLC-stage-D HCC who are ineligible for liver transplantation should receive the best supportive care (BSC), including pain management, palliative radiotherapy for painful bone metastasis, nutrition optimization, and psychological support.	100%	Low
41	Primary prevention of HCC can be achieved with the following: <ul style="list-style-type: none"> <li>– Universal vaccination against HBV infection</li> <li>– Antiviral treatment for patients with chronic HBV and HCV infections</li> <li>– Controlling NASH risk factors such as diabetes and obesity</li> <li>– New evidence of a protective role of coffee consumption and aspirin intake</li> <li>– Secondary prevention of HCC: Early detection and chemoprevention of HCC occurrence or recurrence.</li> </ul>	100%	Moderate

The experts unanimously (100%) agreed that patients with chronic hepatitis C (HCV) infection, especially those with associated liver cirrhosis, are more predisposed to HCC than anyone else in Egypt, owing to its high prevalence in the Egyptian population. The panel members highlighted the fact that patients approaching the age at which they are at risk of developing HCC could be the reason for the increase in the proportion of HCC patients with HCV in Egypt, even after appropriate treatment is administered. However, some panelists believed that the rising incidence rate was expected to reduce in two or three decades. Previous studies reported that the incidence rates of HCV in Egypt were constantly rising, with an estimated increase of 14% in the general population.<sup>12</sup> HCV infection promotes liver fibrosis and cirrhosis, indirectly leading to the development of HCC. HCV also induces liver cell proliferation through viral gene products resulting in hepatic carcinogenesis.<sup>16</sup> The AASLD guidelines highlighted the fact that patients with HCV-associated liver cirrhosis have a 3.5% annual rate of HCC development.<sup>17</sup> The risk of HCC in patients with chronic HCV infection is 15–20 times higher than that in patients without HCV infection.<sup>15</sup>

In 2018, the Egyptian MOH initiated a national screening campaign to contain the high HCV incidence in the country by 2020, following which a direct-acting antiviral (DAA) sofosbuvir-based regimen was provided to all the screened individuals with confirmed HCV infection.<sup>18</sup> Many studies showed conflicting results regarding the outcome of DAA treatment and HCC recurrence exit.<sup>19,20</sup> Given the previous prevalence of HCV and HCC in Egypt, the national HCV treatment program proved the impact of screening and the efficiency of DAA agents in HCV treatment.<sup>1</sup> A majority of the panel members (96.6%) recommended HCC surveillance in patients with cirrhosis post-DAA therapy, even after

HCV eradication. The experts highlighted the importance of screening for HCC at follow-up in patients who have received DAA therapy. Previous studies showed that DAAs are well-tolerated by HCV patients with advanced liver disease and could provide SVR rates >95%.<sup>15</sup> However, some studies revealed that the incidence of de novo HCC in patients with HCV cirrhosis increased with the use of the DAA regimen, which may be attributed to the increasing age, severity of liver disease, and waitlist mortality in liver transplant patients.<sup>15,21</sup> Most guidelines recommended close surveillance in patients with HCV-associated cirrhosis even after DAA therapy and an evaluation of the benefit of viral cure against the recurrence risk.<sup>15,22</sup> The panel members suggested that Egyptian patients with cirrhosis treated with DAA are advised to be followed up every four months. The mandatory screening of patients prior to the initiation of treatment with DAA was suggested. The panelists also stressed the need to raise awareness among patients with cirrhosis to be regularly followed up after receiving DAA therapy.

The panel unanimously recommended that all patients with chronic hepatitis B virus (HBV) infection and liver cirrhosis require HCC surveillance. However, patients with HBV without cirrhosis require HCC surveillance only if they are above 40 years of age, have the hepatitis D co-infection, or have a family history of HCC. All HCC experts recommended surveillance in patients with nonalcoholic fatty liver disease (NAFLD) with significant fibrosis or cirrhosis (F3 or F4). The panel recognized the impact of HBV on HCC development, considering that HBV was associated with 88% of histologic cirrhosis worldwide, most of which developed into HCC.<sup>23</sup> The literature demonstrates the direct impact of HBV on the pathogenesis of HCC and its integration into the host's DNA.<sup>24,25</sup> Although the prevalence of HBV infection is declining in Egypt due to the universal hepatitis B vaccination program, this infection is considered a higher risk for HCC than HCV.<sup>25</sup> A single-center Egyptian study found that HBsAg positivity was an independent risk factor for HCC owing to a two-fold increase in HCC development.<sup>26</sup> Another study found a shift in the risk factor influence between HCV and HBV over a decade; however, the risk of HCC development associated with HBV infection remained higher than that associated with HCV infection during the study period.<sup>25</sup> In Egypt, the seroprevalence of the hepatitis D virus (HDV) was estimated to be 3.4% in the Nile Delta region.<sup>27</sup> However, the prevalence of HCC among people co-infected with HBV and HDV was comparable, ranging from 8.8% to 13.6%.<sup>27,28</sup> International and local studies suggest that a family history of liver cancer is a significant risk factor for HCC development.<sup>29,30</sup> A study by Velazquez reported that the risk of developing HCC in cirrhotic patients above 54 years of age is four times higher than that in younger patients.<sup>31</sup> An Egyptian single-center study demonstrated that cirrhotic patients aged 40–59 years are 3.7 times more likely to develop HCC than others.<sup>25</sup>

The panel members (100%) stated that HCC surveillance is essential in patients with secondary etiologies of cirrhosis, including hereditary hemochromatosis (HH), primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), and alpha 1-antitrypsin deficiency (A1AT). This statement was supported by the AASLD guidelines that recommended HCC surveillance in patients with HH and PBC.<sup>32</sup> In Egypt, several studies have reported the association of HCC in HCV patients carrying hemochromatosis gene (HFE) mutant alleles, such as the A allele at position 346 of the ghrelin gene or the D allele of the H63D mutation.<sup>33,34</sup> However, other studies failed to prove the impact of HFE mutations on the risk of HCC in cirrhotic patients.<sup>35</sup> A study conducted in Sweden reported that patients with HH have a 20 times higher risk for HCC without an increased risk for non-hepatic malignancies.<sup>36</sup> According to the current literature, cirrhosis secondary to PBC increases the risk of HCC occurrence at a level similar to that observed in patients with HCV infection.<sup>37</sup> Although AIH is associated with a significantly lower risk of HCC development compared to other chronic liver diseases,<sup>38</sup> patients with cirrhosis secondary to AIH showed an annual incidence rate of >1.5%, resulting in the need to include such patients in routine HCC surveillance programs.<sup>39</sup> Another study added that HCC occurs in 7% of patients with AIH and cirrhosis of at least a five-year duration, with an incidence rate of 1 per 350 patients-years.<sup>40</sup> Further, a retrospective study revealed that patients with cirrhosis secondary to A1AT deficiency show a 0.88% annual incidence of HCC,<sup>41</sup> which justifies the need for surveillance in such patients. The prevalence of A1AT deficiency in the Egyptian population is not well defined; however, a previous Egyptian study on 100 HCC patients did not prove a significant association between the A1AT mutation and the incidence of HCC.<sup>33</sup>

## Modes of HCC Surveillance

### Consensus Statements

The majority of the panel members (92%) recommended US imaging as the modality of choice for regular HCC surveillance due to its availability and affordability, in spite of its limited reliability in patients with either truncal obesity or marked parenchymal heterogeneity. They recommended surveillance using US and alpha-fetoprotein (AFP) monitoring every four months (to be performed by a qualified physician). Several studies and existing international guidelines supported and recommended US as one of the primary, most effective, non-invasive, sensitive, and affordable imaging modalities for HCC surveillance.<sup>22,42–44</sup> A meta-analysis of 32 studies showed that US had an overall sensitivity of 84% for detecting HCC at any stage and a sensitivity of 47% for the early detection of HCC.<sup>21,45</sup> Another systematic review of 14 studies showed that the pooled estimate of the sensitivity of the US for HCC detection was 60%, and the specificity was 97%.<sup>21</sup> Real-world data from a multicenter study of 374 patients revealed that 42% of the patients with HCC were diagnosed during screening, and the use of US for screening was associated with a higher rate of early tumor detection, a higher rate of curative treatment, and improved survival compared with HCC detected via techniques other than screening.<sup>46</sup> An observational study conducted in Egypt reported that 74% of physicians from university hospitals and 46% of physicians from the MOH considered US the most important HCC screening test.<sup>11</sup> The panelists advocate for the use of AFP, as the current literature proved it is one of the most widely used serological markers in HCC due to its affordability and availability. A plasma concentration of 20 ng/mL as a pathological threshold for diagnosis shows elevated levels of AFP in 60%–80% of hepatic cancers.<sup>21</sup> US alone has a lower sensitivity for any-stage and early-stage HCC than when combined with AFP. AFP alone was reported to have low specificity, as elevated levels could be recorded in liver cirrhosis, chronic hepatitis, neurodegenerative diseases, and non-seminomatous testicular cancer. Therefore, a combination of both diagnostic tools was recommended.<sup>21</sup> Previous studies in Egypt also supported the combined use of ultrasonography and AFP ( $\geq 200$  ng/mL) monitoring for the diagnosis of HCC.<sup>25</sup> A study conducted in Egypt on 514 patients with chronic HCV infection proved that the combination of AFP monitoring and ultrasonography could improve HCC surveillance.<sup>30</sup> The study highly recommended a national surveillance program for the detection of HCC in cirrhotic HCV Egyptian patients by combining AFP monitoring and ultrasonography.<sup>30</sup>

The panelists stressed the use of quality equipment and qualified physicians to perform ultrasound imaging. This recommendation was based on the current literature demonstrating that multiple factors, such as the screening frequency, the physician's experience, and the patient's disease status, are known to determine the effectiveness of ultrasonography.<sup>45</sup> A study in the USA revealed that US sensitivity ranged between 35% and 84% depending on the equipment used and the operator's expertise.<sup>21</sup> A study conducted in Egypt reported that the accuracy of US is highly dependent on the operator's ability to discriminate HCC from non-neoplastic lesions (regenerative nodules),<sup>30</sup> therefore, the panelists emphasized the importance of using trained personnel to perform ultrasonography and obtain accurate results. International societies, including the AASLD, EASL, and APASL, recommended surveillance for adults with cirrhosis and high-risk patients without cirrhosis using US with or without AFP at six-month intervals. The surveillance interval is decided according to the patient's clinical status, available resources, and affordability.<sup>14,15</sup> Studies have shown that performing surveillance every six months increases the sensitivity for detecting early-stage HCC to 70%.<sup>14</sup> Considering the increasing prevalence of HCC and its associated risk factors in Egypt, the panelists recommended a surveillance interval of four months.<sup>45</sup>

## Diagnosis, Staging, and Risk Assessment

### Laboratory Diagnosis

#### Consensus Statements

There was a 90% agreement among the panel members that proteins induced by Vitamin K Absence-II (PIVKA-II) and AFP-L3 can be considered in conjunction with US every four months, depending on the availability and affordability. Some experts suggested that PIVKA-II and AFP-L3 are more sensitive yet expensive than AFP; however, some panelists referred to them as cost-effective. Most experts stated that their use would depend on their availability in the country. The literature supports the statement stating that AFP, the AFP-L3 fraction, and PIVKA-II/DCP are the three primary tumor markers for HCC with recommended cut-off values of 10 ng/mL, 10%, and 40 mAU/mL, respectively.<sup>45</sup> A study



conducted among patients with Child-Pugh classes A and B revealed that a combination of AFP monitoring and ultrasonography increased the sensitivity in detecting early-stage HCC from 32% to 65%.<sup>14</sup>

The AASLD and EASL guidelines do not recommend AFP alone as a screening test due to its relatively inadequate sensitivity and specificity for surveillance, low positive predictive value, and inadequate accuracy for early-stage HCC.<sup>12,22</sup> However, the KLCA-NCC and APASL surveillance recommendations support AFP use with US.<sup>47</sup> Thus, AFP and US may play complementary roles once combined. The efficiency of the surveillance method varies as per the onset and incidence of HCC in the region.<sup>47</sup> A previous study recommended an AFP threshold of 400 ng/mL as a suitable cut-off level for detecting HCC, regardless of its combination with ultrasonography. However, there was no correlation between elevated serum AFP levels and the tumor size or number in the previous study conducted in Egypt.<sup>30</sup>

All (100%) panelists agreed on the inclusion of biomarkers such as PIVKA-II and AFP-L3 in conjunction with US in the follow-up of HCC after treatment considering the fact that currently, AFP-L3 is approved by the FDA for liver cancer assessment as part of the GALAD score (a tool to address the heterogeneity in biology among the etiologies of cirrhosis).<sup>14,21</sup> According to the experts, the biomarkers (PIVKA-II and AFP-L3) are prognostic tools. AFP is known to have low specificity and can be elevated in non-HCC conditions. As mentioned earlier, AFP-L3 (the lens culinaris agglutinin-reactive fraction of AFP) demonstrated superior diagnostic efficacy in HCC.<sup>48,49</sup> A previous study reported that elevated AFP-L3 levels could predict early HCC even in the absence of elevated AFP.<sup>50</sup> A study carried out on 80 Egyptian patients evaluating the role of AFP-L3 as a biomarker revealed that AFP-L3 had a higher sensitivity than AFP and could serve as a diagnostic biomarker for detecting early-stage HCC.<sup>51</sup>

PIVKA-II has been an accepted biomarker for HCC surveillance and is currently included in evidence-based Japanese and APASL clinical guidelines.<sup>45</sup> In a study conducted in Egypt on 83 patients, PIVKA-II was highly sensitive, specific, and superior to AFP monitoring in the early detection of HCC patients. It also demonstrated the ability to differentiate between the histopathological grades of HCC, evaluate the thrombosis of the portal vein, and categorize the early and late stages of HCC.<sup>52</sup> A pilot study conducted in Europe concluded that the PIVKA-II could be added to the routine panel of HCC tumor markers as it achieved better sensitivity than AFP.<sup>53</sup> Another study conducted in Egypt on 441 HCC patients at a hospital concluded that with abnormal AFP levels ( $\geq 400$  ng/mL), the serum AFP level remains useful, whereas AFP-L3 is more specific than AFP in the diagnosis of HCC using AFP levels ( $<400$  ng/mL).<sup>54</sup>

Some panelists (75%) encouraged the adoption of screening scores such as GAAD (Gender, Age, AFP, DCP) and GALAD (Gender, Age, AFP, DCP, AFP-L3). However, some (17.39%) experts did not agree and highlighted the need for additional studies to identify the optimum score and validate the tools to be used in the early detection of HCC. This recommendation was based on the results of several international studies demonstrating that a combination of biomarkers is possibly the best tool for HCC detection. Multiple studies support the use of the GALAD score, which the FDA approved for the early detection of HCC in March 2020.<sup>55,56</sup> A study conducted in Europe demonstrated that the GALAD score outperforms the biomarkers AFP, DCP, and AFP-L3 used alone for the early-stage detection of HCC in Caucasian patients with chronic hepatitis B or C. The score displayed a robust performance in identifying HCC patients independent of the tumor burden, the extent of the liver disease, and the viral load.<sup>57</sup> A study conducted in the United States demonstrated the superiority of the GALAD score compared to US and recommended its use in patients with advanced-stage hepatic dysfunction or obesity who are at risk of false-negative US findings.<sup>58</sup> No specific studies on the use of these scores in the Egyptian population have been reported so far. The panelists recommended that additional prospective and observational studies on the validity of these scores to use in the early detection of HCC are essential.

## Radiological Diagnosis

### Consensus Statements

\* *Except for Hemangioma*

Imaging techniques are crucial in managing patients with detected nodular hepatic lesions. All panelists (100%) recommended that in at-risk patients, the recognition of a nodule measuring  $>10$  mm using US should be followed by multiphase CT or contrast-enhanced MRI with diffusion as currently, all existing international guidelines recommended multiphase CT or MRI with extracellular contrast agents or hepatobiliary contrast agent (HBA)-enhanced MRI as first-line diagnostic imaging modalities for at-risk patients.<sup>47</sup> Studies have shown that multiphase CT is suitable for HCC

diagnosis because of its lower cost, faster imaging times, and lower technical complexity.<sup>59,60</sup> The experts suggested using multiphase CT and dynamic MRI with diffusion and strongly insisted that MRI is superior to CT when performed appropriately. Dynamic studies are essential to visualize the hemodynamic and histopathological characteristics of HCC and differentiate typical hypervascular HCC from other hypervascular benign lesions or false positives.<sup>47</sup> The choice of imaging modality should be made after considering the clinical scenario, technical advantages, limitations, and local practices. So, the experts suggested that the choice of one technique over the other should be individualized.

Most experts (95.24%) recommended that multiphase CT and MRI exams could be performed, interpreted, and reported through the CT/MRI Liver Imaging Reporting and Data System (CT/MRI LI-RADS), as some studies demonstrated that CT/MRI LI-RADS for the diagnosis of HCC could be applied to multiphase CT or MRI performed in patients with cirrhosis.<sup>29,61</sup> Lesions are divided into eight distinctive LI-RADS categories reflecting the chances of HCC according to the presence or absence of primary features (non-rim APHE, non-peripheral portal venous or delayed-phase washout, enhanced capsule appearance, a size of at least 1 cm, threshold growth of more than 50% in less than six months), and additional factors.<sup>62</sup>

As diagnostic tools, MRI and CT have high sensitivity and specificity for HCC diagnosis.<sup>63–66</sup> The current literature shows that MRI has sensitivity and specificity of over 90% each for lesions >2 cm, and for all-size lesions, its per-patient sensitivity and specificity are 88% and 94%, respectively.<sup>59,67</sup> Studies have shown that CT/MRI images are attained for the differential diagnosis of US-detected lesions. The LR-1 and LR-2 category of LI-RADS includes simple cysts to distinctive nodules (<2cm) without any malignant features.<sup>62</sup> The LI-RADS detection score designations help regulate the need for more frequent surveillance or additional imaging. For lesions measuring 10–20 mm, expert radiologists suggested the use of either CT or MRI; however, other panelists recommended using both techniques. Thus, all experts (100%) recommended the use of a single imaging technique (CT or MRI) to confirm the typical vascular pattern for lesions measuring 10–20 mm based on the available evidence and recommended approach of the LI-RADS for CT and MRI.<sup>62</sup>

The LI-RADS recommends US-based surveillance in LR-1 observations and CT-scan or MRI for lesions in the category of LR-2 as they are simple cysts with no major features favoring malignancy.<sup>62</sup> All (100%) panelists recommended that liver nodules measuring either <1 cm or 1–2 cm (LI-RADS criteria 1 or 2) should be followed by US after three months. The LI-RADS 3 category includes lesions with an intermediate probability of HCC (38% HCC; 40% malignancy).<sup>62,64</sup> The recommendation for managing such lesions is as per the multidisciplinary discussion. Most of the experts (88.24%) agreed that for such lesions, the approach to management would include follow-up imaging (if the lesion measures <2 cm), imaging with an alternative modality (of alternative contrast agent), and biopsy. There was no preference for any specific technique, as the clinical practice and tailored approach were the deciding factors. The LI-RADS can categorize and characterize abnormal liver lesions and enable the radiological diagnosis of HCC in patients with cirrhosis. However, liver biopsy is still recommended for diagnosis in patients without cirrhosis.<sup>62</sup> Percutaneous liver biopsy can be considered when the diagnostic imaging results are unclear, including in patients with cirrhosis and nodules of hypovascular nature, as the AASLD and EASL guidelines support liver biopsy in the diagnosis of HCC.<sup>17,22,68</sup>

### Staging and Assessment of HCC

Most panelists (88.24%) recommended using the Barcelona Clinic Liver Cancer (BCLC) staging system as it offers the most prognostic information, including an assessment of the tumor burden, liver function, and patient survival. It is widely and officially accepted by the EASL, AASLD, and other international societies<sup>69</sup> and is reported to have the best correlation with patient outcomes.<sup>70</sup> It includes four elements: tumor extension, liver functional reserve, physical status, and cancer-related symptoms. Its algorithm classifies HCC into five stages depending on the disease status, Child-Pugh score, and ECOG PS.<sup>68,69</sup> Each stage in this system is allocated a treatment recommendation from the currently available options, distinguishing this staging system from the others. Various studies conducted in Egypt use the BCLC staging system for performing clinical studies.<sup>30,52</sup> A study conducted in Egypt on 2000 patients revealed that BCLC was the best at discriminating the survival of patients in distinct stages and had the greatest homogeneity of survival among patients within the same stage, confirming that it is a good prognostic system.<sup>71</sup> Several studies conducted in Italy and China revealed that the BCLC classification is the best predictive model for HCC patients receiving radical therapy, including percutaneous ablation or surgical resection.<sup>72–75</sup> A trial conducted on 3892 HCC patients in Taiwan revealed

that the treatment regimens determined by the BCLC classification are beneficial and reasonable for survival.<sup>76</sup> The BCLC staging system also proved to be of significant prognostic value in HCC patients with early- to advanced-stage tumors treated with multiple modalities as per the investigations from Egypt, South Korea, Spain, Italy, and the USA.<sup>69</sup> All studies show that the predictive accuracy of the BCLC classification is highly established and independent of the tumor stage, treatment modality, underlying liver disorder, and environmental differences.<sup>77</sup>

All panelists recommended sub-classifying the Intermediate Stage BCLC-B into three or four subgroups according to the liver status, the number of lesions, and the type of lesions (infiltrative) to facilitate treatment decisions associated with the heterogeneity of patients in this stage. Studies revealed that the subclassification of stage B into Stages B1–B4 was proposed by Bolondi (2013)<sup>78</sup> in association with multiple first-line and alternative treatment options. The subclassification was also validated externally in a cohort of HCC patients in South Korea and Taiwan.<sup>79,80</sup> In 2016, another subclassification of the BCLC-stage B into three sub-classes, as per the Child-Pugh score plus Milan and up-to-7 criteria, known as the “Kinki Criteria”, was reported.<sup>81</sup>

A majority of the panelists (95%) recommended the adoption of the ALBI score, the Child-Pugh score, and the MELD score for the assessment of liver status before HCC treatment. They emphasized the need to raise awareness of the use of the albumin/bilirubin (ALBI) score among the medical community. Some experts advocated that many clinical trials use only the Child-Pugh score to evaluate the liver status before treatment. The BCLC model of classification used the Child-Pugh score, and the MELD is an independent predictor of mortality in patients with HCC.<sup>81</sup> The suggestion to use the ALBI score was based on the evidence from the literature confirming that the ALBI score is one of the standard measures to assess liver function in patients with HCC. It uses only objective parameters (albumin and total bilirubin) that assist in its superior evaluation, regardless of its complex calculation, which may limit its applicability.<sup>82</sup> The ALBI score is calculated from the archived laboratory work-up using the following equation:  $ALBI\ score = (\log_{10}\ bilirubin \times 0.66) + (albumin \times -0.085)$ .<sup>83,84</sup> The prognostic performance of the Child-Pugh-based BCLC is used to assess the hepatic reserve function along with the BCLC and ALBI grade is similar. A previous study revealed that the ALBI score is suitable for BCLC-B (intermediate-stage disease) cases to overcome survival heterogeneity.<sup>85</sup> The modified intermediate liver cancer criteria (MICAN), a sub-grading for the BCLC-B using the ALBI score, has shown good ability over the other systems in the prognosis of BCLC-B patients, including those treated with transarterial chemoembolization (TACE).<sup>85</sup>

Most of the panelists (75%) recommended upper GIT endoscopy before systemic therapy or surgery for any HCC patient. Some physicians disagreed with the need for an endoscopic assessment prior to HCC therapy. Furthermore, some experts suggested endoscopic assessment only in patients who have not had a recent endoscopy prior to treatment. The panelists advocating endoscopic assessment before systemic therapy or surgery in HCC patients stated that endoscopy and the measurement of the portal vein tension are essential for treatment stratification. Previous studies reported gastrointestinal bleeding as an adverse effect of systemic therapies.<sup>86–89</sup> Studies supporting endoscopic assessments prior to HCC treatment included case reports demonstrating the use of endoscopy in treating hard-to-reach HCC lesions.<sup>90,91</sup> Hsu et al recommended upper endoscopy before systemic therapy in patients with cirrhosis (with or without portal hypertension) to assess the risk of variceal and non-variceal bleeding.<sup>92</sup> Further research on the utility of endoscopy in the management of HCC is recommended.

## Management of HCC

### Multidisciplinary Teams in HCC

#### Consensus Statements

All (100%) panelists agreed that a multidisciplinary team (MDT) is essential for the management of HCC. HCC has diverse presentations that are compounded by the liver disease status, and multiple treatment options are available. An MDT composed of all specialists delivering different therapies can help improve patient outcomes. A balanced, individualized, and unbiased treatment selection is ensured when specialists from many different fields discuss the benefits and risks of the available treatment.<sup>93</sup> Studies have shown that in HCC patients, the diagnosis, staging, and treatment selection are challenging and influenced by the increased prevalence, genetic heterogeneity, multiple etiologies, and concomitant chronic liver diseases.<sup>94</sup> An MDT approach ensures that the disease is staged correctly and that the treatment recommendations are patient-centered, evidence-based, and arrived at by consensus. Several studies reveal that

the multidisciplinary management of HCC patients improves survival and reduces disease-related mortality. A retrospective cohort study of newly diagnosed HCC patients revealed that the 5-year survival rate was significantly higher in patients managed by an MDT compared to those not managed by a team.<sup>94</sup> A hospital-based prospective study conducted in Egypt demonstrated improved management of HCC through an MDT decision.<sup>95</sup> According to the literature, an MDT should include hepatologists, medical and surgical oncologists, transplant surgeons, diagnostic and interventional radiologists, pathologists, radiation oncologists, nurses, supportive care specialists, and palliative physicians.<sup>96</sup> All members play an essential and active role as their expertise is required to provide optimum care for HCC patients.

### Resection and Ablation in HCC Treatment

The majority (94.44%) of the panelists recommended surgical resection in HCC patients with Child-Pugh Class A liver function without clinically significant portal hypertension integrated with ALBI and/or p-ALBI. Multiple studies and literature reviews indicate that in patients with adequate liver functional reserves, potentially curative hepatectomy is an optimal treatment option for HCC.<sup>68</sup> Patients with a preserved liver function and HCC confined to the liver with no evidence of portal hypertension and the invasion of hepatic vasculature are ideal for surgical resection. Also, patients with Child-Pugh Class A cirrhosis, with normal bilirubin levels and well-preserved hepatic functions, can safely undergo hepatectomy. In selective HCC patients, relapse-free long-term survival rates (40%) and improved five-year survival rates (up to 90%) were reported.<sup>97</sup> A study conducted in two Egyptian centers reported improved three-year survival rates with hepatectomy and concluded that it is an effective therapeutic tool in Child-A score HCC patients with well-compensated livers.<sup>98</sup> The practice of resection in patients with significant portal hypertension is controversial, with portal hypertension in cirrhotic patients being considered a contraindication to surgical resection by some authors.<sup>99,100</sup> The ALBI score could predict the risk of post-hepatectomy liver failure more accurately than the Child-Pugh scores in HCC patients after liver resection.<sup>101,102</sup> The panelists advocated its integration into clinical practice. Several existing guidelines also recommend liver resection in well-compensated patients.<sup>22,32</sup>

The majority of panelists (88%) recommended that unresectable lesions measuring up to 4 cm be subjected to local ablative therapy by radiofrequency ablation (RFA) or microwave ablation (MWA), as several studies demonstrate the safety and efficacy of RFA and MWA in treating unresectable colorectal liver metastases near large vessels or major bile ducts. The safety and efficacy of RFA in unresectable hepatic lesions measuring less than 6 cm have been depicted by several studies, some of them reporting that the best outcomes are achieved in single tumors measuring <4 cm.<sup>93,103,104</sup> RFA is considered a suitable treatment approach for unresectable lesions because of its efficacy, reproducibility, low complication rates, and availability. A cohort study and three independent meta-analyses, including five RCTs, advocate improved results, especially in patients with tumors measuring 2–5 cm in terms of local tumor control and survival benefits with RFA.<sup>105–108</sup> Studies support the use of MWA as its benefits include an improved convection profile, higher constant intra-tumoral temperatures, faster ablation times, and the ability to use multiple probes for the simultaneous treatment of multiple lesions.<sup>103</sup> MWA is generally preferred when the tumor measures  $\geq 3$  cm or if the nodule is closer to large vessels, independent of its size.<sup>103</sup> Previous studies supported the use of MWA to treat unresectable HCC.<sup>109</sup> A meta-analysis of seven RCTs concluded that both RFA and MWA have similar mortality, safety, and efficacy outcomes in treating HCC.<sup>110</sup> However, a significant advantage of MWA over RFA is that the treatment outcome with MWA is not influenced by the tumor site.<sup>68,111</sup> An RCT conducted in Egypt revealed no significant difference between outcomes obtained from RFA and MWA in HCC patients, except for the shorter time required for ablation.<sup>112</sup>

### Trans-Arterial Chemo-Embolization (TACE) and Its Associated Combinations in HCC Treatment

TACE is recommended by a majority of the panelists (88.89%) in hypervascular HCCs classified as BCLC-B: well-defined non-infiltrative HCC lesions with a tumor burden of less than 50% of the total liver volume as several existing international guidelines, including the AASLD, ESMO, EASL, SAUDI, and INASL, recommend the use of TACE as the primary treatment option for BCLC-stage B HCC.<sup>15</sup> The BCLC classification also recommends TACE for intermediate-stage HCC.<sup>113</sup> Two randomized controlled trials<sup>114,115</sup> and meta-analyses<sup>115,116</sup> demonstrated the survival benefits of TACE in comparison to the best supportive care in patients with multinodular and/

or large HCC, no cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread. Several studies and literature reviews conducted in Egypt also reported the use of TACE as the primary treatment in stage B patients, increasing the median survival of such patients to 20 months.<sup>93,117,118</sup> A single-center study conducted on 221 patients with locally-advanced HCC treated with TACE in Egypt showed a median OS of 16 months and a median PFS of 6 months, demonstrating that TACE has good survival rates in such patients with noticeable toxicities. The study emphasized the appropriate selection of patients to improve outcomes with TACE.<sup>119</sup>

A majority (95.24%) of the panelists recommended that single lesions measuring 4–6 cm, beyond the local ablative therapy and unfit for surgical resection and transplant, could benefit from combined heat ablation with chemoembolization. Some studies revealed that in patients with HCC, a combination of TACE and RFA is associated with a significantly higher OS and recurrence-free survival than RFA monotherapy, especially in lesions measuring >3 cm.<sup>22</sup> The literature also recommended that thermal ablation and TACE could be combined if the tumor size exceeds 5 cm, allowing for ablations of up to 6 cm with good response rates.<sup>113</sup> A retrospective study conducted in Egypt on 22 patients ablated using TACE-RFA and 45 patients ablated with TACE-MWA, all with unresectable HCC lesions <5 cm and Child-Pugh Class A-B, demonstrated that the combination techniques are more effective with TACE-MWA showing a higher response rate than TACE-RFA in lesions measuring 3–5 cm. There was no significant difference in the survival rates between the two groups.<sup>120</sup> Some experts suggested the addition of lesions measuring up to 8 cm; however, other panelists disagreed as there is insufficient evidence to support the use of the combination for such big lesions. The panelists agreed that in a combination treatment approach, chemoembolization needs to be done prior to ablation to reduce the size of the lesion. However, a combination of the two techniques may appear to be demanding in terms of resources.

The different scoring systems provide additional support in deciding if a patient is eligible for TACE and deciding the further course of treatment during TACE. The STATE (Selection for TrArterial chemoembolization TrEatment) score and the HAP (Hepatoma Arterial-embolization Prognostic) score, with its modifications (mHAP-II and mHAP-III), have been specially devised to assist in deciding if treatment with TACE is suitable for a patient.<sup>113</sup>

The STATE score, which consists of serum albumin, tumor burden (up-to-7 criteria), and the CRP level, states that patients with lower scores have a significantly impaired median OS (5.3 months vs 19.5 months) and are not recommended to be treated with TACE.<sup>121</sup> The HAP score includes AFP levels, tumor size, and serum levels of albumin and bilirubin. It categorizes patients into four subgroups, and the values of the individual factors help decide if the patient is eligible for treatment with TACE.<sup>122</sup> The external validation of these two scores by some studies shows that they have a moderate ability to predict individual patients' prognoses.<sup>123</sup> A multicenter study concluded that the HAP score is best suited for screening patients prior to initial TACE.<sup>124</sup> All panelists (100%) suggested using the STATE score and HAP score for stratification before TACE based on the relevant literature; however, they did not recommend basing clinical decisions on the scores alone.

A multivariate analysis<sup>125</sup> investigated TACE repeated for a second or third time and identified three prognostic factors, which are an increase in the aspartate aminotransferase level by >25%, an increase in the Child-Pugh score, and the absence of tumor response. These factors were imbedded into an "ART" score, and patients with an ART score of 0–1.5 points were noted to be the ones who benefited most from a second TACE. Patients with a higher score of  $\geq 2.5$  showed significantly impaired survival and were associated with more adverse events after the second TACE treatment.<sup>125,126</sup> A multicenter study concluded that the ART score is a validated prognostic score in patients with intermediate-stage HCC undergoing TACE and improves the early detection of chemoembolization failure.<sup>124</sup> All panelists (100%) suggested using the ART score post-TACE based on the relevant literature.

### Trans-Arterial Radio-Embolization (TARE) in HCC Treatment

TARE demonstrates a good safety profile and promising efficacy in disease control and involves using the selective intra-arterial administration of microspheres loaded with a radioactive compound such as yttrium-90.<sup>127</sup> The ESMO defined TARE as a promising and suitable therapeutic option for patients with diffuse intrahepatic tumor spread or a "bridging" therapy.<sup>128</sup> The NCCN recommends TARE for patients with liver-confined HCC who are not eligible for transplantation or resection.<sup>129</sup> Studies involving selective patients with intermediate-stage HCC reveal that tumor shrinkage performed

to reduce the disease burden and allow for resection or transplantation was better with TARE than with TACE.<sup>130,131</sup> The current literature supports the downsizing of tumors in selected patients with a large disease and moderate residual liver volumes using TARE.<sup>127</sup> Accordingly, all panelists (100%) recommended using TARE in patients with a large tumor burden beyond TACE procedures.

Previous studies demonstrated that treatment with TARE achieved an OS of up to 23.2 months in patients with portal vein thrombosis involving segmental or lobar branches, BCLC-stage C HCC.<sup>132,133</sup> All panelists (100%) recommended the use of TARE in patients with segmental or partial portal vein thrombosis. Most experts agree that TARE is a cost-effective treatment and must be reserved for patients who are ineligible for TACE. A study conducted in Egypt was performed for ten months in two University Hospitals on 86 HCC patients using the conventional TACE with either doxorubicin or TARE Y-90 using glass microspheres. It revealed that in intermediate-stage HCC patients, both treatments resulted in similar survival probabilities despite more advanced disease in the TARE-Y 90 group of patients. The study concluded that patients in the TARE Y-90 group were associated with shorter hospitalization periods and fewer treatment sessions, and the treatment was well-tolerated.<sup>134</sup>

### Liver Transplantation in HCC Treatment

Liver transplantation (LT) is the best treatment option for patients with decompensated cirrhosis. In HCC, LT allows for the removal of the primary tumor and treats hepatic insufficiency.<sup>135</sup> Living donor transplantation is one of the strategies used to overcome the organ shortage in LT. More than 300 liver transplants have been performed annually from living donors in Egypt. The transplants from deceased donors are rare in the country despite the approval for the same by the Egyptian Parliament in 2010.<sup>136</sup> LT is recommended as the first-line treatment option for HCC within the Milan criteria, which is a benchmark for selecting HCC patients eligible for LT. Patients with T2 stage criteria are considered eligible for LT, while those beyond this stage are considered only after a successful downstaging into the Milan criteria. The literature demonstrates that the UCSF criteria (single nodule  $\leq 6.5$  cm or 2–3 nodules  $\leq 4.5$  cm and a total diameter  $\leq 8$  cm),<sup>137,138</sup> Up-to-7 criteria (Lesions with number 7 as the sum of the size (cm) of the largest tumor and the number of tumors)<sup>139</sup> have non-significant differences compared to the Milan criteria in terms of post-LT-survival and have been externally validated.<sup>22</sup> A review stated that it was ethically acceptable for LDLT to be offered to patients with tumors exceeding the Milan criteria.<sup>140</sup> The evidence supports the recommendation by all the panelists (100%) that the expansion in transplantation criteria using different staging systems such as the UCSF and the “up-to-7” criteria can be applied to LT in Egypt.

In neoadjuvant treatments, downstaging is defined as the treatment applied to bring patients with a tumor burden outside the accepted criteria for transplantation within the acceptable criteria.<sup>141</sup> Several studies accepted patients as LT candidates when their HCC was successfully down-staged to within the Milan criteria.<sup>142–144</sup> The panelists suggested that the recommended interval to monitor tumor behavior after downstaging into the acceptance criteria is between 6–18 months. All panelists recommended a six-month monitoring interval after downstaging and before the LT, as 18 months was alleged to be a long time. Studies depict several AFP cut-off levels in the transplant criteria; however, there has been no common consensus in any existing guidelines on how to combine them with the structural characteristics of HCC. All panelists (100%) suggested an AFP cut-off level of  $<1000$  ng/mL before transplantation based on their clinical practice. Some literature reviews and studies also supported using a cut-off level of  $<1000$  ng/mL; however, more data are required.<sup>142,145</sup> The experts also highlighted the need to study the impact of systemic therapy after downstaging and before LT to reduce the recurrence of the disease.

### TACE Failure in HCC Treatment

The literature stated that the repeated application of TACE results in the emergence of new lesions, a consistent increase in the levels of tumor markers, and a gradual decrease in liver function with reduced tumor necrosis. Molecularly targeted therapies are now available, and the repetition of TACE can be avoided after TACE failure, which makes it essential to define it. The JSH first published the criteria for TACE failure in 2011 and 2014 and defined it as a failure to control the tumor in the target lesion or the appearance of new lesions after  $\geq 2$  consecutive TACE sessions.<sup>45</sup> Other criteria defining

TACE refractoriness include the Taiwan criteria and the International Expert Panel (EPOI HCC) Criteria (A. L. Cheng et al, 2014), which state that patients who need two or more TACE sessions within 6–12 months should be regarded as TACE failure and switched to molecularly targeted agents. The criteria proposed by Raoul (2014) also recommended switching to the next systemic treatment if there is no response after two TACE sessions.<sup>146</sup> The definition of TACE failure is known to differ from one country to another. According to several studies, existing guidelines, and the current literature, intermediate-stage patients showing disease progression or poor tolerance after the first or second TACE should be migrated to systemic therapy, preferably Sorafenib,<sup>93,147,148</sup> as it preserves the liver function and reduces the incidence of extrahepatic or vascular invasion.<sup>149–151</sup> Based on the available evidence on the importance of recognizing TACE failure and considering the next available treatment in patients with TACE refractoriness, and the earlier recommendation of using the ART score post-TACE to determine whether or not the patient can benefit from a subsequent TACE, all panelists (100%) recommended that patients with an ART score of >1.5 after the first TACE or two consecutive imaging findings of non-response or evidence of decompensation should be considered for next-stage migration to systemic therapy.

### Systemic Therapy in HCC Treatment

All panelists (100%) recommended the following sequence of systemic therapy for HCC: First-line treatment with atezolizumab/bevacizumab or sorafenib or lenvatinib; second-line treatment after immunotherapy or with TKIs such as regorafenib, cabozantinib, and ramucirumab.

The Phase 3 IMbrave-150 trial showed that patients with unresectable HCC had better OS and PFS with atezolizumab/bevacizumab than with sorafenib. The one-year OS was 67.2% (95% CI, 61.3–73.1) with atezolizumab/bevacizumab compared to 54.6% (95% CI, 45.2–64.0) with sorafenib. The median PFS values were 6.8 months (95% CI, 5.7–8.3) and 4.3 months (95% CI, 4.0–5.6), respectively. The JSH guidelines recommended a combination of atezolizumab plus bevacizumab as first-line treatment for unresectable advanced HCCs that cannot undergo surgical resection, loco-regional therapy, LT, or TACE in patients with Child-Pugh A (good PS and liver function) based on positive results from the IMbrave-150 trial.<sup>152</sup> The ESMO guidelines state that atezolizumab plus bevacizumab showed superiority to sorafenib in terms of efficacy in patients with advanced HCC. It was recommended as the standard of care in the first-line therapy of patients with advanced HCC and approved by the EMA in 2020.<sup>153</sup>

Another LOE was available for sorafenib (a multi-tyrosine kinase inhibitor, TKI) as an alternative first-line treatment for advanced-stage HCC, being the first drug to be approved in 2007.<sup>22,45,68,154</sup> The highly acclaimed SHARP study (OS 10.7 months with sorafenib vs 7.9 months with placebo) and the Asia Pacific study (OS 6.5 months with sorafenib vs 4.2 months with placebo) led to the approval of sorafenib as the first-line treatment of patients with Childs A cirrhosis and unresectable or metastatic HCC.<sup>155–157</sup> The EASL guidelines recommended sorafenib for advanced tumors, BCLC-stage C, or tumors progressing despite loco-regional therapies. It recommended maintaining sorafenib therapy until radiographic progression is observed and, later, second-line treatment with regorafenib.<sup>22</sup> Previous studies also demonstrated that sorafenib is of greater benefit in HCC patients with underlying HCV infection compared to HBV infection.<sup>158</sup>

The REFLECT trial comparing lenvatinib (a multi-tyrosine kinase inhibitor) to sorafenib in the first-line therapy of unresectable HCC showed that lenvatinib was non-inferior to sorafenib in terms of OS.<sup>159</sup> The results demonstrate that lenvatinib provides clinically significant benefits to patients with a well-preserved liver function (Child-Pugh A class), good performance status, advanced tumors, BCLC-C without main portal vein invasion, or biliary ducts invasion or >50% liver occupation by tumors or tumors unsuitable for or progressing despite loco-regional therapies.<sup>159</sup> Several existing guidelines recommend using lenvatinib in the first-line treatment setting.<sup>22,153</sup> However, the JSH clinical practice guidelines for HCC 2017<sup>160</sup> recommended sorafenib or lenvatinib as second-line therapy for Child-Pugh Class A patients who fail treatment with first-line therapy due to intolerable side effects or radiographic progression.<sup>45</sup>

Regorafenib was reported to be effective as a second-line agent for prolonging survival in patients with HCC who tolerated sorafenib by the RESORCE trial.<sup>161</sup> Ramucirumab was approved in June 2019 to treat HCC in patients with an AFP level of  $\geq 400$  ng/mL based on results from the REACH-2 study.<sup>162</sup> According to the study of Llovet et al, who conducted a pooled analysis of the REACH II study, ramucirumab survival benefit in patients with very aggressive HCC (AFP  $\geq 400$  ng/mL) was (HR: 0.64; 95% CI: 0.49–0.84) and in nonviral advanced HCC, it was (HR: 0.56; 95% CI: 0.40–0.79).

Cabozantinib was approved based on the results of the CELESTIAL trial. It has been evaluated in the second and third-line treatment after intolerance to or progression under sorafenib treatment. The efficacy and safety of cabozantinib depend on the duration of sorafenib pretreatment.<sup>163</sup> All panelists recommended the first-line and second-line therapies based on the existing guidelines and studies proving the efficacy of the molecularly targeted agents in the treatment of HCC.

A single, high priming dose of tremelimumab (anti-cytotoxic T lymphocyte-associated antigen 4) plus durvalumab (anti-programmed cell death ligand-1) showed encouraging clinical activity and safety in Phase 2 and 3 trials of advanced HCC.<sup>164,165</sup> Moreover, the combination of tremelimumab and durvalumab has been reported to be superior to sorafenib, adding another first-line treatment option. According to BCLC 2022, tremelimumab with durvalumab can be administered as first-line systemic therapy in patients with advanced HCC with an expected survival of >2 years.<sup>166</sup> If atezolizumab-bevacizumab or tremelimumab with durvalumab are not feasible, sorafenib, lenvatinib, or durvalumab can be administered as a first-line therapy.<sup>167</sup> Lenvatinib and single-agent durvalumab are non-inferior to sorafenib, but it is essential to mention that there is a significant need to evaluate whether the current second-line alternatives maintain their efficacy in patients initially receiving any of these options. Sorafenib, lenvatinib, or durvalumab may be beneficial following atezolizumab-bevacizumab or tremelimumab/durvalumab, but it is important to determine whether they should be regarded “de facto” second-line alternatives or if their efficacy may be altered in this setting.<sup>167,168</sup>

Adjuvant therapy aims to decrease the incidence of HCC recurrence in patients who undergo surgical resection. The use of adjuvant systemic therapy following resection, transplantation, or loco-regional ablation drew the attention of oncologists and hepatologists treating patients with HCC. A majority (92.86%) of the panelists recommended that systemic treatment can be used as an adjuvant treatment in certain circumstances, such as the presence of evidence of microvascular invasion in a resected liver with HCC. A large Phase III trial (the STORM trial) was conducted to assess the use of Sorafenib as an adjuvant treatment in patients with resected HCC. It revealed no difference in the RFS between the two groups after 12.5 months, showing that sorafenib treatment was associated with increased adverse events, including four deaths.<sup>169</sup> A network meta-analysis revealed that the addition of adjuvant therapy lowers the risk of recurrence and provides survival benefits after surgical resection indicated for HCC.<sup>170</sup> Based on the poor evidence supporting adjuvant treatment in routine clinical practice, all (100%) panelists do not recommend adjuvant therapy in HCC and suggest further studies to prove its benefit to be included in routine practice. The panelists recommended that all the proposed studies should be carried out in Egypt.

### Treatment Assessment in HCC

According to previous oncology trials, tumor response is generally measured as per the RECIST (Response Evaluation Criteria in Solid Tumors) criteria. The EASL and AASLD guidelines adopted a modified version of the RECIST criteria. The treatment response accounted for the induction of intra-tumoral necrotic areas in estimating the decrease in the tumor load and not just the reduction in the overall tumor size.<sup>100,171</sup> Several clinical studies have demonstrated that the objective response measured by mRECIST predicts survival in patients receiving loco-regional therapies.<sup>172</sup> A meta-analysis identified seven clinical trials using mRECIST response to assess the survival outcomes after loco-regional treatments.<sup>173</sup> Only two clinical trials have evaluated the objective response in systemic therapies by mRECIST,<sup>174,175</sup> and more research in this area is essential. A trial conducted on 30 HCC patients in Egypt used the mRECIST criteria to assess the radiological response.<sup>176</sup> The EASL guidelines recommended evaluating the response to locoregional therapy with mRECIST and systemic therapy with both RECIST and mRECIST criteria.<sup>22</sup> Based on the evidence from the literature, existing guidelines, and clinical trials, all (100%) panelists recommended using the mRECIST Criteria to assess the progression and radiological response after HCC management. Although no existing guideline or literature describes the optimum time to assess the disease progression after immunotherapy, all (100%) panelists recommended a time of 12 weeks or four cycles of immunotherapy to assess the disease progression based on their clinical practice.

Some trials and series have reported the efficacy and tolerability of different external beam radiotherapy techniques in distinct stages of HCC treatment.<sup>177</sup> A meta-analysis of trials of TACE alone versus TACE plus external beam radiotherapy demonstrated significant benefits with the combination therapy for the post-treatment OS and local tumor control.<sup>178</sup> Additional data on the efficacy of TARE and external beam radiotherapy is known to be emerging. Despite



the signs of efficacy and safety, there exists a need for large prospective studies to assess the role of radiotherapy in HCC. The available evidence supporting this therapeutic approach in HCC management is low. Based on the available literature, all (100%) panelists suggest using external beam radiotherapy in HCC treatment only under special indications, where local thermal ablative techniques are contraindicated, or in HCC recurrence following RFA or TACE.

### Combination Therapy in HCC Treatment

Several prospective controlled studies evaluated the efficacy of combination treatment, including sorafenib plus TACE, for intermediate and advanced-stage HCC treatment, and the overall results appeared promising.<sup>93</sup> According to previous studies, the combination of sorafenib and TACE has an acceptable safety profile; however, there were no conclusive data on the efficacy of the combination.<sup>179–181</sup> TARE, in combination with systemic therapy, is under investigation.<sup>22</sup> A single-center retrospective study of 104 HCC patients with BCLC-stage B/C reported that TACE plus Sorafenib improved the OS compared to Sorafenib alone.<sup>182</sup> Prolonged PFS and OS, and a significantly increased tumor response rate depicting potential efficacy, were noted in the study comparing and evaluating the benefits between the two groups—sorafenib alone and sorafenib plus TACE.<sup>182</sup> A multicenter retrospective real-world study conducted in China demonstrated that regorafenib combined with TACE was beneficial and tolerable in patients with unresectable HCC.<sup>183</sup> Based on the currently available evidence, all panelists (100%) supported the use of combination therapy in HCC management.

### Palliative Care in HCC Treatment

All panelists recommended that patients with BCLC-stage-D HCC who are not eligible for liver transplantation should receive the best supportive care (BSC), including pain management, palliative radiotherapy for painful bone metastasis, nutrition optimization, and psychological support. The recommendation was based on evidence from all international hepatology societies suggesting the use of palliative support, including pain management, nutrition, and psychological support in HCC patients with BCLC-stage D or Child-Pugh Class C who are not eligible for LT.<sup>22,45,68</sup> The life expectancy of such patients is about 3–4 months, and the disease management is only symptomatic.<sup>184</sup> An ideal palliative care team includes liver and palliative care physicians and nurses, allied healthcare practitioners (physiotherapists, pharmacists, and dieticians), counselors, and other staff.<sup>2</sup> The best supportive care is selected for patients whose disease is not responsive to active treatment or who are too sick to receive such therapy. The EASL guidelines recommended the use of paracetamol (up to 3 g/day) or opioids (avoiding NSAIDs); palliative radiotherapy for painful bone metastases; active enhancement of the nutritional status; psychological support (non-pharmacological); QOL for both the patient and their family, and the importance of engaging an appropriately trained palliative care team to provide optimum management in this terminal stage.<sup>22</sup>

### Prevention of HCC

According to the current literature, the prevention of HCC depends on the early prevention of risk factors (primary prevention), the treatment of risk factors at an early stage (secondary prevention), and the prevention or decrease in the rate of HCC relapse after successful curative treatment (tertiary prevention).<sup>185,186</sup> Primary prevention of HCC is the only sustainable and practical method to decrease the associated disease burden. Vaccination against hepatitis B reduces the risk of HCC and is recommended for all newborns (within 24 hours) and high-risk groups by the WHO.<sup>187</sup> The panelists mentioned that HBV vaccination is mandatory in Egypt and suggested a universal vaccination against HBV infection as one of the strategies to prevent HCC. In Egypt, the HBV vaccination program and HCV eradication through the national campaign are the two approaches adopted to prevent HCC. The EASL guidelines recommended antiviral treatment for patients with chronic HBV and HCV infections.<sup>22</sup> Direct-acting antivirals were introduced in Egypt through the efforts of the government and the National Committee for the Control of Viral Hepatitis. The 100 “Million Healthy Lives” initiative treated millions of patients with HCV with a cure rate of over 90%.<sup>1</sup> The speed, scale, and quality of the Egyptian initiative were praised by the WHO representatives. More than 60 million Egyptians were screened, and 4 million HCV patients were treated between 2014 and 2020.<sup>7</sup> Therefore, all panelists (100%) also recommended the same for the prevention of HCC.

HCC surveillance is a secondary prevention strategy to decrease the burden of HCC through early tumor detection and management of the disease. It needs to be complemented by primary prevention and development and utilization of chemo-preventive strategies. A national follow-up program was established for patients with cirrhosis to encourage the early detection of HCC.<sup>7</sup> All panelists (100%) advocate secondary prevention strategies for the prevention of HCC.

The burden of HCC associated with NAFLD and NASH is increasing in many countries. Metabolic diseases such as diabetes and obesity are also associated with an increased risk for HCC.<sup>188</sup> The current literature supports the recommendation of all (100%) experts who control lifestyle-related modifiable factors such as changing dietary patterns, increased physical activity, reduced alcohol consumption, and avoiding certain food items can help prevent HCC related to NAFLD and NASH.<sup>188</sup> The panelists advocated that patients with diabetes, obesity, and cardiovascular disorders may benefit from chemoprevention along with lifestyle modification based on a pooled analysis of two prospective studies showed that the regular use of aspirin (650 mg) per week was associated with a 50% reduction in risk of HCC.<sup>189</sup> New evidence on the association between the regular consumption of coffee and a decreased risk of fibrosis development in NAFLD<sup>190</sup> was also noted and suggested as a prevention strategy for HCC.<sup>191</sup>

## Conclusion

The recommendations presented in this report represent measures taken at the highest-level HCC treatment centers in Egypt and were developed by an expert panel consisting of hepatologists, oncologists, gastroenterologists, surgeons, pathologists, and radiologists, under the umbrella of the ESLC. The recommendations were based on the country's currently available local diagnostic aids and treatment methods and suggested future prospects. The recommendations serve as guidance to all stakeholders involved in HCC management in Egypt, the Middle East, and the African region. Areas of future research were identified, including several potential collaborations to support and improve clinical practice at different Egyptian institutes. The panel suggested a routine follow-up and update of the guidelines.

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