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REVIEW ARTICLE

Screening, Surveillance, and Management of Hepatocellular Carcinoma During the COVID-19 Pandemic: a Narrative Review

Sami Akbulut[1,2] · Ibrahim Umar Garzali[1,3] · Abdirahman Sakulen Hargura[1,4] · Ali Aloun[1] · Sezai Yilmaz[1]

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Abstract

Purpose The COVID-19 pandemic has been a burden to the global community as a whole but the healthcare community had bore the brunt of it. The pandemic resulted in policy changes that interfered with effective healthcare delivery. The healthcare community attempted to cope with the pandemic by triaging and prioritizing emergency conditions especially COVID related, ahead of elective conditions like cancer care. There was also fear that patients with cancer were at an increased risk of sever COVID-19 with increased mortality. Hepatocellular carcinoma (HCC) was also affected by these policies.

Methods We reviewed the modified measures adopted in screening, surveillance, and management of HCC during the pandemic using PubMed, Medline, Index Medicus, EMBASE, SCOPUS, and Google Scholar databases.

Result The main modification in surveillance and screening for HCC during the pandemic includes limiting the surveillance to those with very high risk of HCC. The interval between surveillan was also delayed by few months in some cases. The adoption of teleconferencing for multidisciplinary team meetings and patient consultation is one of the highlights of this pandemic all in an effort to reduce contact and spread of the virus. The treatment of early-stage HCC was also modified as needed. The role of ablative therapy in the management of early HCC was very prominent during the pandemic as the surgical therapy was significantly affected by the lacks of ventilators and intensive care unit space resulting from the pandemic. Transplantation, especially living donor liver transplantation, was suspended in few centers because of the risk of infection to the living donors.

Conclusion As we gradually recover from the pandemic, we should prepare for the fallout from the pandemic as we may encounter increased presentation of those patients deferred from screening during the pandemic.

Keywords Hepatocellular carcinoma, Liver resection · Liver transplantation · Screening, Surveillance · COVID-19 pandemic

Introduction

The only constant thing in healthcare is change and the evolutionary change the healthcare community underwent to contain the COVID-19 was enormous [1]. While most changes are evolutionary, occurring slowly overtime, some changes can be revolutionary caused by a sudden need for adaptation to an event of grave danger in healthcare both to the patients and providers of healthcare. Such was the situation the world found itself when the COVID-19

✉ Sami Akbulut
akbulutsami@gmail.com

Ibrahim Umar Garzali
gazaliumar270@yahoo.co.uk

Abdirahman Sakulen Hargura
caxulen04@yahoo.com

Ali Aloun
dr.alialoun85@hotmail.com

Sezai Yilmaz
sezai.yilmaz@inonu.edu.tr

[1] Department of Surgery and Liver Transplant Institute, Faculty of Medicine, Inonu University, Elazig Yolu 10 Km, Malatya 44280, Turkey

[2] Department of Public Health, Faculty of Medicine, Inonu University, 44280 Malatya, Turkey

[3] Department of Surgery, Aminu Kano Teaching Hospital, Kano 700101, Nigeria

[4] Kenyatta University Teaching, Referral and Research Hospital, Nairobi 00100, Kenya

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(SARS-CoV-2) virus infection was reported in China in December 2019 [2]. The virus rapidly spread and it was declared a pandemic by the World Health Organization (WHO) in March 2020 [3]. As of 6 March 2022, there were 433 million COVID-19 cases reported globally with 5.9 million deaths across the globe according the WHO COVID-19 dashboard [4]. Response of the global community included enacting measures to curtail the spread of the virus which included decisions like social distancing and stay-at-home/lockdown orders [2, 3, 5, 6]. The healthcare community was also forced to redistribute resources towards the care of the patients with COVID-19 infection. The decision by the global community and the healthcare community had direct effect on the care of patients with chronic diseases and cancers [6–13]. There was significant reduction in all non-COVID-19-related care in the hospitals and the lockdown orders resulted in reduction in patients' presentation to the hospital for the non-emergency diseases [6–13]. This has resulted in reduction in screening and diagnosis of cancers, including hepatocellular carcinoma (HCC) [6–14].

Although COVID-19 is a predominantly pulmonary disease, it also affects the liver, which according to published studies, the general incidence of liver damage during or after COVID-19 infection ranges from 10.5 to 69% [15–18]. Abnormalities in liver enzymes have been documented in up to 78% of patients with COVID-19 by Kudo et al. [16]. It is believed to cause liver injury directly by binding to angiotensin-converting enzyme-2 (ACE-2) receptor expressed by hepatocyte and cholangiocytes. It also causes injury to hepatocytes through indirect methods. It causes severe hypoxia in patients with pulmonary disease and this will cause injury to the hepatocytes. The liver injury is usually transient and resolves spontaneously, but in patients with background chronic liver disease, it may result in decompensation [15, 16]. HCC was also deeply affected by the COVID-19 pandemic as multiple studies have reported delays in screening, surveillance, diagnosis, and delays or alteration in treatment plan [15, 16, 19–22]. The aim of this review is to identify the modifications implemented by various scholars in the management of HCC during the COVID-19 pandemic and accelerated measures to counter possible increase in advanced disease brought on by COVID-19 disruptions.

Methods

Literature search was conducted by three independent researchers. We conducted a literature search in PubMed, Medline, Index Medicus, EMBASE, SCOPUS, and Google Scholar databases using the following keywords in various combinations: Hepatocellular Carcinoma, Liver resection, Liver transplantation, Ablative therapy, Bridging therapy, Screening, Surveillance, and COVID-19 pandemic. Only studies published in English were included. Related articles and reference list were also searched manually to avoid omission. The titles of the studies were screened and abstract evaluated for inclusion. Only full, original articles written in English were selected. National, regional, and international guidelines were also included in the narrative review.

Screening and Surveillance of HCC During the COVID-19 Pandemic

As recommended by the American Association for the Study of Liver Diseases (AASLD) and European Association of the Study of Liver Disease (EASL), deferring HCC surveillance by 2–3 months during times of limited radiologic capacity, such as those experienced during the COVID-19 pandemic, is likely safe [7, 9].

Most guidelines recommend semi-annual HCC surveillance using abdominal ultrasonography (US), with or without alpha-fetoprotein (AFP), in high-risk individuals. This has been associated with increased early detection and improved survival among hepatitis B virus (HBV) patients and patients with cirrhosis [7, 9].

However, during COVID-19 pandemic, elective imaging was deferred, including HCC surveillance [23, 24]. This could be based on studies that showed patients with cancer appear to have increased mortality due to COVID-19 infection, with mortality rates ranging from 11 to 28% [25, 26]. In patients with COVID-19 infection, HCC surveillance should be deferred until recovery [15, 19, 27, 28]. However, it is worth noting that these deferments in screening and surveillance measures pose risks of inevitably delayed presentations resulting in advanced liver diseases, especially HCC, that may not be visible yet [29, 30].

Surveillance of High-Risk HCC Patients

Prioritizing HCC surveillance for those with the highest risk may be needed [22]; however, the risk stratification may be difficult as there are no models universally applicable to all patients.

There are risk stratification models both among HBV patients and cirrhosis patients. To date, there has been limited validation of most models, so their clinical utility in routine practice has remained limited. The following patients are universally considered at risk of HCC [31–33]:

1. Patients with chronic HBV infection with or without cirrhosis
2. Patient with chronic HCV infection with cirrhosis
3. Patient with cirrhosis from any etiology

Patients with combinations of high-risk features may be considered the highest priority for surveillance, whereas surveillance may be deferred in those with 1 or no risk factors [22]. Older age and male gender are consistent components of most HCC risk stratification models. Child-Turcotte-Pugh (CTP) score and presence of portal hypertension are other important risk factors for HCC. Finally, the cause of the liver disease is a consistent risk factor, with active viremia associated with a 3–6% annual risk, whereas patients with alcohol-related liver disease, nonalcoholic steatohepatitis, or hepatitis C virus (HCV) cirrhosis after viral cure have a lower annual risk of 1–2% [13, 14, 22, 30, 33, 34].

Some liver transplant centers have suspended or limited transplants to those with high Model for End-Stage Liver Disease (MELD) scores; however, the listed population could be considered a priority for surveillance [3, 8, 11, 22, 24, 32, 34]. Early detection of HCC is critical in this population to prevent waitlist dropout, and timely identification of HCC lesions allows patients to accrue waiting time with MELD exception [20]. Surveillance can provide other information relevant to decision-making regarding transplant, such as development of portal vein thrombosis [14, 15, 22, 35].

Patients with CTP class C cirrhosis who are not transplant eligible should not be subject to surveillance because of the risk of liver-related mortality [12, 14, 34, 36]. Also, patients with other significant comorbidities like cardiovascular diseases or malignancies that limit life expectancy or treatment eligibility should not be subject to surveillance. Surveillance can also be waived in certain groups at lower risk during the pandemic (e.g., HCV or nonalcoholic steatohepatitis [NASH] patients) in absence of cirrhosis, given marginal risk–benefit ratio [12, 14, 34, 36]. Preventing over surveillance in populations unlikely to benefit is a practical way to minimize harms of surveillance, including possible COVID-19 exposure. However, patients that were deferred from initial screening should be followed up through teleconsultation and if there is need for physical evaluation, they are invited to come to the clinic [14–16, 19, 28].

Timing of Surveillance and Choice of Surveillance Test

Surveillance for HCC is recommended to be done every 6 months because the tumor doubling time is said to be around 4–6 months [11, 32–34]. The surveillance test of choice has been USS with or without AFP. The use of USS with or without AFP has a sensitivity of 68% for detection of HCC early [32–34]. As recommended by AASLD and EASL, deferring HCC surveillance by 2–3 months during times of limited radiologic capacity, such as those experienced during the COVID-19 pandemic, is likely safe [5, 7, 9, 22].

With the global community enacting social distancing laws, the ability to safely perform USS has been affected and this may require some modifications to ensure reduced contact between the sonologist and the patients. One of the modifications proposed was that the sonologist should be fully kitted with personal protective equipment (PPE) and the patients should have a mask on during the procedure. At the end of the procedure, the machine should be scrubbed down with antiseptic [5, 7, 9, 22].

Another effort at reducing this contact was the use of magnetic resonance–based surveillance. This is not considered cost-effective if applied to the all cirrhotic patients [22]. To reduce contact and comply with social distancing, the use of blood-based marker as a surveillance tool has been considered. Only AFP of > 20 ng/ml has been validated for use as a blood-based screening tool for surveillance of HCC, but its sensitivity and specificity are not adequate for it to be use alone [37]. Tayob et al. [37] proposed the longitudinal measurement of serum AFP at different intervals to increase its sensitivity and specificity. But this may be counterproductive during the pandemic as this may require frequent hospital visit for the test to be conducted [6, 32, 37].

A single blood-based biomarker has been considered inadequate; hence, a combination panel of biomarkers and sociodemographic factors proposed by Jonson et al. [38] can be used as a surveillance tool during the pandemic. The panel is called GALAD and it combines gender, age, lectin reactive alpha-fetoprotein (AFP-L3), AFP, and des-gamma carboxyprothrombin (DCP) [31]. The panel has demonstrated sensitivities of 60–80% for early-stage detection in large multinational case–control studies, including recent data among NASH patients. GALAD has shown superior performance to the component biomarkers, in part related to inclusion of gender and age in the biomarker algorithm.

Diagnosis of HCC During the COVID-19 Pandemic

Diagnosis of new cases HCC was noticed to drastically reduce during the COVID-19 pandemic [6, 8, 11–13]. This was attributed to the global mandates of lockdowns and the reduction of elective services in the healthcare community which resulted in the following [6, 8, 11–14, 35, 39, 40]:

1. Delay consultations of patients their general practitioner
2. Decreased referral by other professionals because of fear of COVID-19 infection
3. Reduced access to diagnostic tools, operating theaters, and intensive care unit (ICU)
4. Travel limitation which prevented patients from other areas reaching medical centers

The diagnostic algorithm of HCC should be maintained as much as possible so as to enable early diagnosis of lesions amenable to definitive care [7, 9, 22, 24, 41]. If the screening and surveillance USS reveal a lesion, it should be considered for further imaging in order to establish the diagnosis. For HCC, contrast-enhanced imaging like multidetector computed tomography (MDCT) and/or magnetic resonance imaging (MRI) can be diagnostic [7, 9, 22, 24, 41].

Various guidelines have given similar pathways in diagnosis of lesions seen in the surveillance US. If the lesion is less than 10 mm, most guidelines do not recommend further imaging but close follow-up of 2–3 months with the US. For lesions larger than 10 mm, there is a need to carry out further contrast-enhanced imaging for diagnosis; while enhanced MDCT/MRI can be diagnostic in most HCC due to the characteristic arteria phase hyper-enhancement and venous wash out, some lesions may require repeat imaging and/or biopsy to confirm diagnosis [7, 9, 22, 24].

In the pandemic era, to minimize exposure, close follow-up re-imaging can be considered for Liver Imaging Reporting and Data System 3 (LI-RADS 3) lesions, whereas further imaging can be done for atypical LI-RADS 4 [7, 42]. Biopsy should be preserved for LI-RADS 4 cases where further imaging is not fruitful as it not only carries increased risk of contact exposure but also poses the risks of disease seeding [42]. Moreover, CT chest should be inculcated into the initial diagnostic contrast-enhanced MDCT to assess for the risk of COVID-19 in high-risk areas [10, 19, 22]. The guidelines-based diagnostic algorithm of HCC for USA (AASLD), Europe (EASL), and Asia (APASL) is shown in Figs. 1 [17], 2 [43] and 3 [44] respectively.

Treatment of HCC During the COVID-19 Pandemic

The management algorithm of the modified Barcelona Clinic Liver Cancer (BCLC) staging system adapted to the COVID-19 era is presented in Fig. 4 [21, 45]. The treatment protocol arranged accordingly to the BCLC stage of HCC in the era of COVID-19 is presented in Fig. 5 [46]. The treatment of HCC is a multidisciplinary endeavor and the decision on the treatment offered is usually decided at multidisciplinary team (MDT) meetings [19]. Patients with early stage A and B benefit from curative treatment of transplant, resection, or ablation. The more intermediate stages benefit from TACE or TARE [7, 9, 22, 41, 47]. The advanced and terminal stages require systemic therapy and best supportive care respectively. Once the pandemic hit the healthcare community, deviation during the management of HCC became necessary.

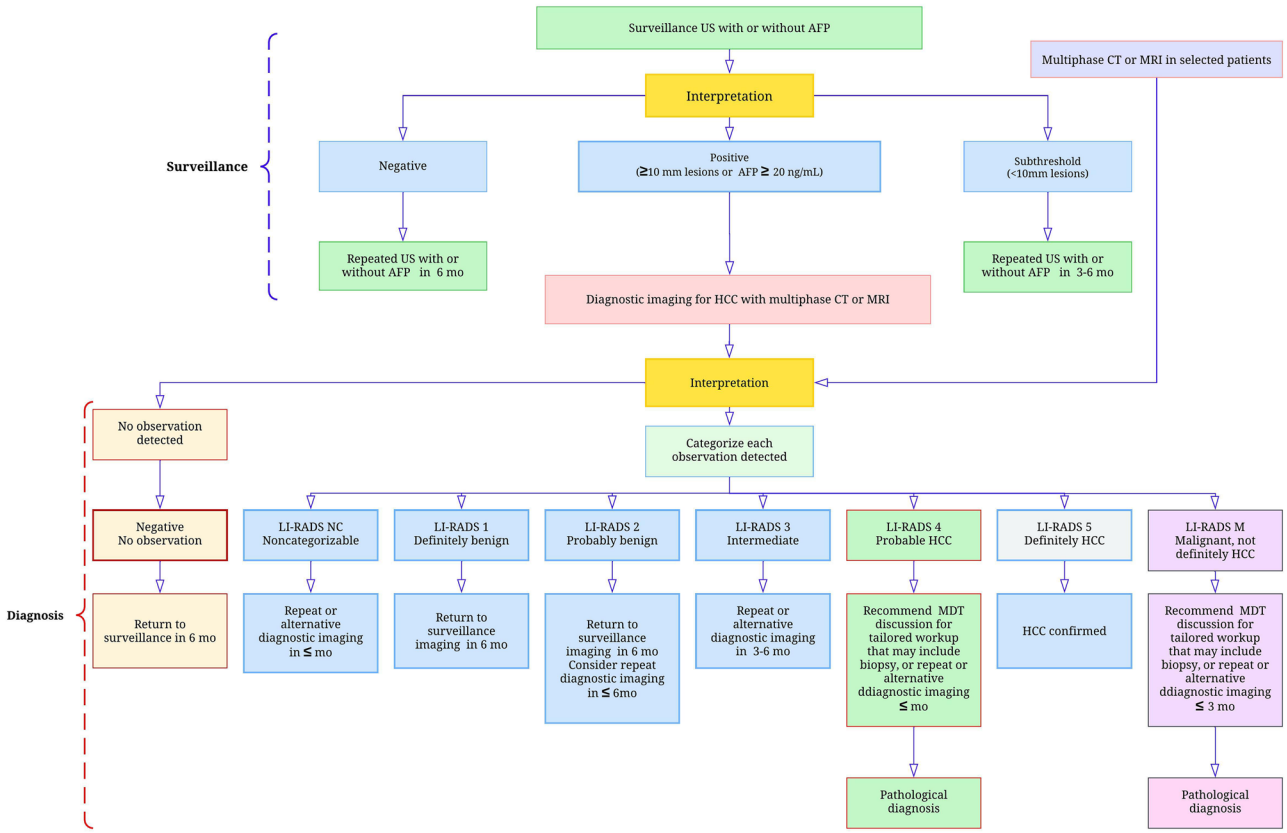

Fig. 1 Surveillance and diagnostic algorithm proposed by AASLD for patients at risk for HCC [17]

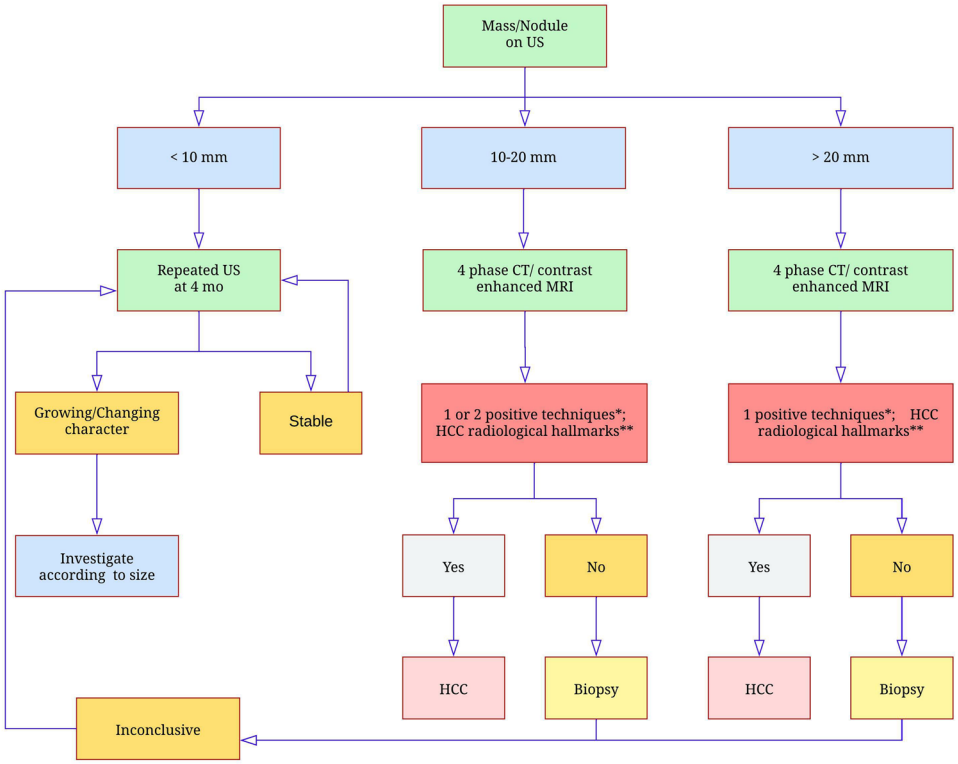

Fig. 2 Diagnostic algorithm of EASL guideline for nodule (mass) by detected US in patients at risk of HCC [43]

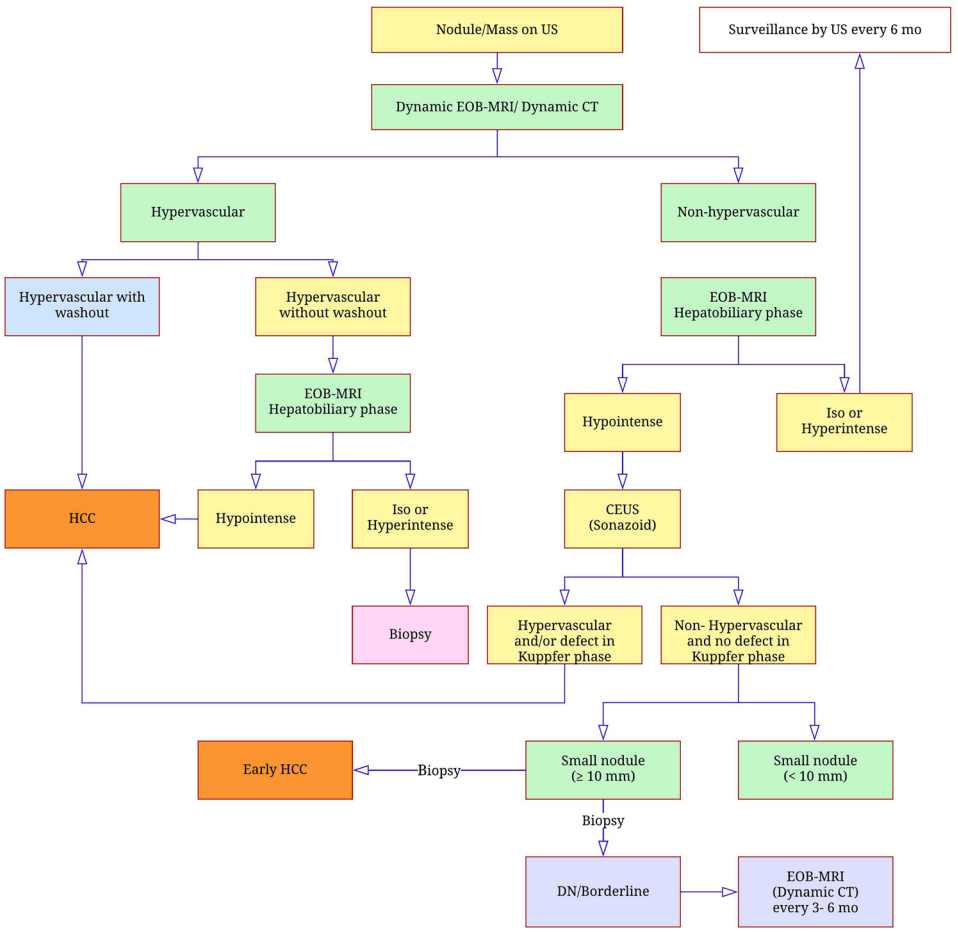

Fig. 3 Diagnostic algorithm of APASL guideline for nodule (mass) by detected US in patients at risk of HCC [44]

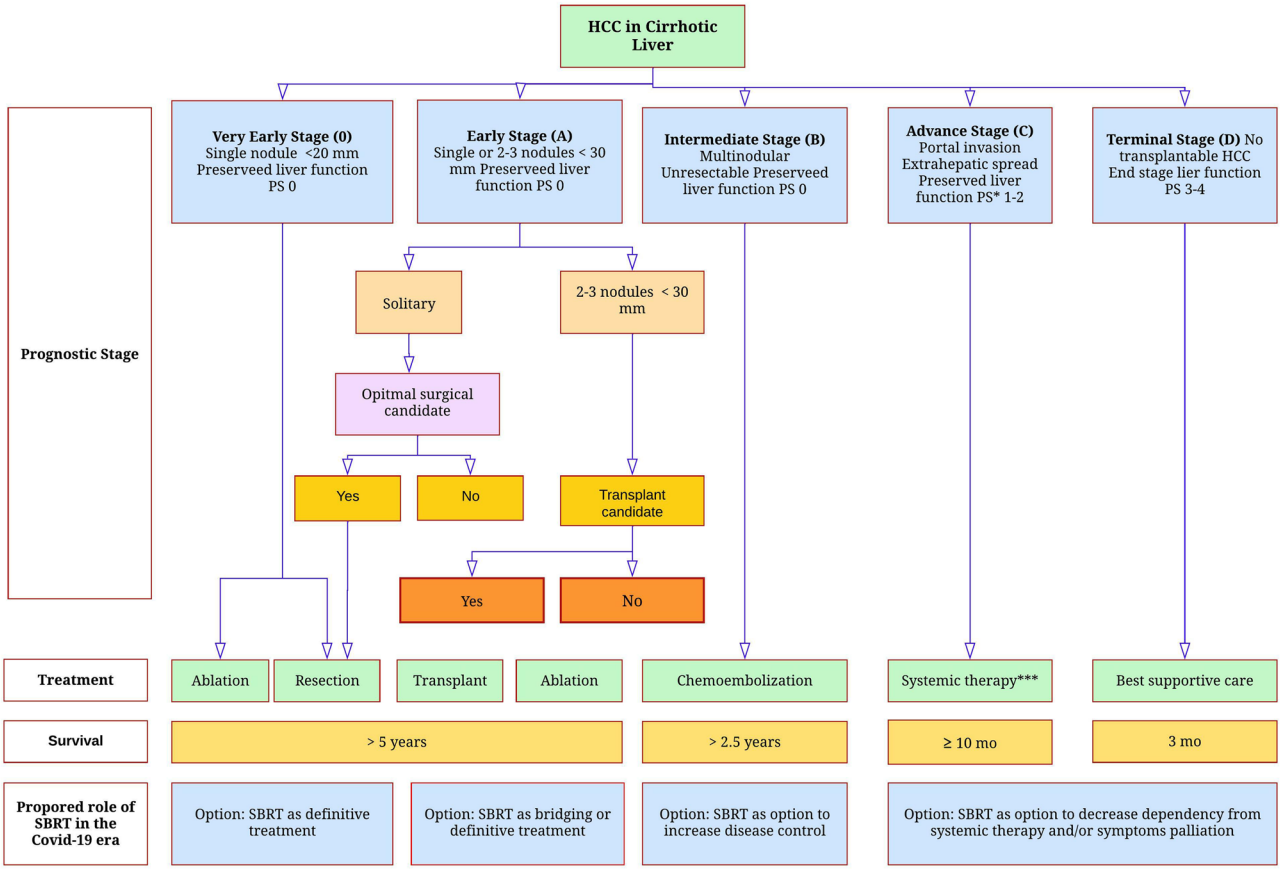

Fig. 4 Modified Barcelona Clinic Liver Cancer (BCLC) staging system–based treatment algorithm during the COVID-19 pandemic (HCC: hepatocellular carcinoma; PS: performance status; SBRT: stereotactic body radiotherapy) [21, 45]

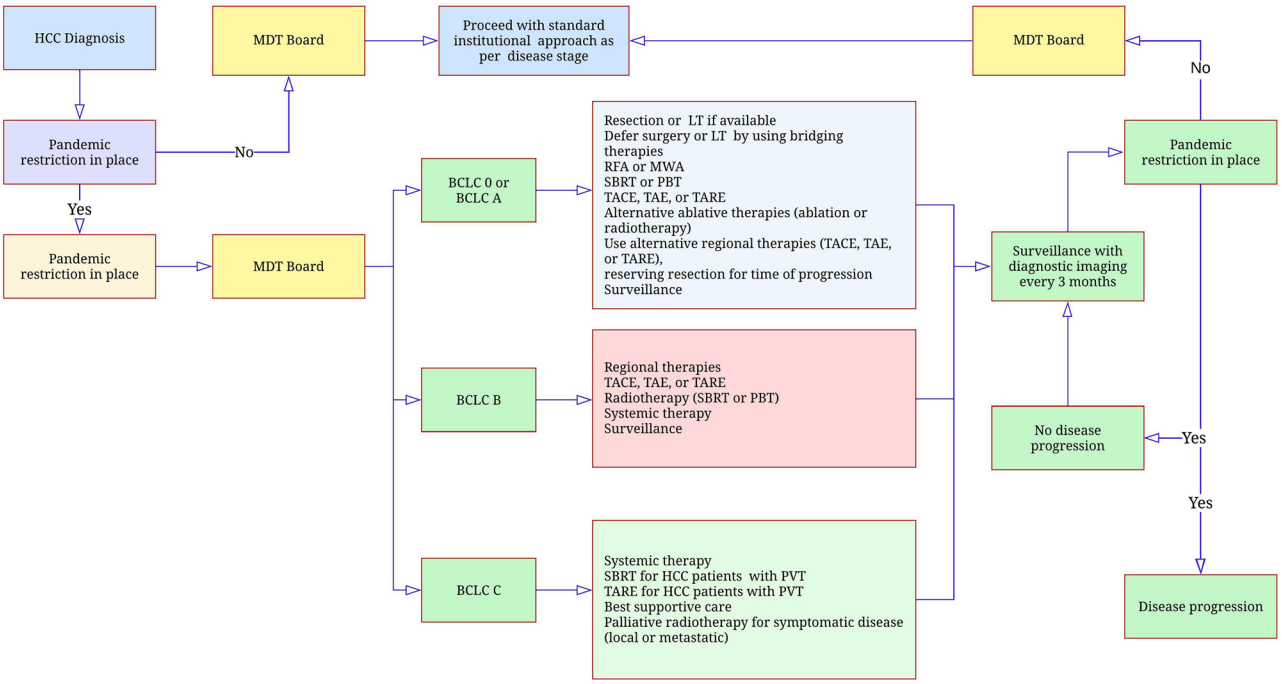

Fig. 5 Proposed treatment pathway for hepatocellular carcinoma during the COVID-19 pandemic (LT: liver transplantation; SBRT: stereotactic body radiotherapy; PBT: proton beam therapy; RFA: radiofrequency ablation; MWA: microwave ablation; TARE: transarterial radioembolization; TACE: transarterial chemoembolization. TAE: transarterial embolization) [46]

All the specialties involved in treatment of HCC were adversely affected by the COVID-19 pandemic. The effect on cancer services included reduced access to the operating room, chemotherapy, radiation therapy, diagnostic imaging, and shortages of personal protective equipment [5, 28, 41, 46, 47]. It has also become routine to discuss with patients the risk of infection with COVID-19, because the combination of cancer diagnoses and comorbidities might result in a possible increase in the morbidity and mortality related to COVID-19.

Guidelines on cancer management have been drafted by the international cancer organization like the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO). Specific guidelines on HCC have also been published by AASLD, EASL, and the International Liver Cancer Association (ILCA).

Multidisciplinary Team During COVID-19

Multidisciplinary team tumor meetings between different specialties are preferably switched to web-based meetings as part of social distancing measures [13, 15]. Radiological features play a crucial role in deciding the treatment modality for HCC: online discussion of imaging, together with clinical information, should be able to help shortlist or decide the suitable treatment modality for most patients [13, 15].

Treatment of Very Early/Early-Stage HCC During the COVID-19 Pandemic

HCC management is generally guided by stage of the disease based on the size of the lesion, the performance status of the patients, and the extent of the underlying chronic liver disease that may limit certain aggressive treatment option [7, 9, 41].

Surgical Resection The burden of COVID-19 on health system that caused strain on the theaters and intensive care units resulted in delays in surgical operations and disrupted subsequent postoperative care that may require ICU management [16, 19, 21, 22, 28]. Faced with these shortages, studies and guidelines published during the pandemic have stressed the need to prioritize patients with smaller disease burden for surgery [5, 7, 9, 15, 27]. Generally, curative liver resection should not be delayed. However, in cases of high risk of decompensation or comorbidities, surgical intervention should be postponed or alternative therapy such as ablation should be adapted [5, 7, 9, 15, 27].

Liver Transplantation Liver transplantation is a curative treatment option for HCC that meets the Milan criteria. Liver transplantation was also affected by the pandemic as the availability of cadaveric donor dwindled. The reduction in cadaveric donor was attributed to two main reasons. [15, 48–50]:

1. Reduction in the number of brain dead donors due to pandemic-related ICU bed occupancy
2. The morbidity/mortality associated with liver transplant operation itself

Transplantation should be decided on case-by-case basis. Patients with poor short-term prognosis, like high MELD score and HCC at the upper limits of the Milan, should be prioritized and delay is not recommended [15, 19, 22, 35, 48–51]. Elective living donor liver transplantation was suspended in some centers because of the risk of COVID-19 infection to the healthy donor while on admission [40, 52, 53]. Therefore, while transplant is still a consideration, other alternative management for early disease and bridging treatment should be prioritized to delay disease progression during the organ shortage.

Our Experience at High-Volume Liver Transplant Center During the pandemic, at our Inonu University Liver Transplantation Institute, we made the adaptation of the existing guidelines as follows [3]:

1. Liver transplantation in adults was performed only if it met the following criteria: (i) transplant candidates with a MELD score > 19, (ii) candidates with HCC that have tumors within Milan criteria and tumor diameter > 2 cm (in the first months of the pandemic), (iii) patients with primary sclerosing cholangitis with 3 or more cholangitis attacks within the last 3 months, (iv) patients whose condition worsened in the last 3-month follow-up (10% or more increase in the MELD score during the follow-up period); (v) furthermore, patients with intractable ascites with or without respiratory distress.
2. Liver transplantation in children was performed only if it met the following criteria: (a) children with pediatric end-stage liver disease scores (PELD) score > 11 points, (ii) children with hepatoblastoma, (iii) children with biliary atresia who have undergone Kasai operation and have had an attack of cholangitis in the prior 2 months, (iv) children with metabolic disease who had 2 or more episodes of decompensation in the last 6 months.

However, in mid-2021 with the reduction in the COVID-19 cases, the institution slowly reverted to the standard guidelines for liver transplantation but we continue to do COVID-19 tests for every living liver donor and recipient before the surgery as a precaution.

Ablative Therapy Percutaneous ablative therapies such as radiofrequency ablation (RFA), microwave ablation (MWA), stereotactic radiotherapy (SRT), and ethanol injection are minimally invasive therapies with potential cure [7, 9, 22]. They are easily repeatable for recurrence. Curative ablation should not be delayed. In patients with three or fewer tumors, each smaller than 30 mm, and of Child–Pugh class A or B, ablation can be used instead of resection [5, 15, 19, 21, 24, 27–29, 39].

Bridging Therapy Bridging traditionally describes the treatment of accepted transplant patients within Milan criteria to mitigate the risk of list dropout while on the waiting list. Locoregional therapy techniques such as ablation and vascular embolization have been employed to achieve this goal, particularly in patients with an expected waiting time of more than 6 months [54].

However, some studies have propose that neoadjuvant therapies can also be used to bridge patients while they wait for surgery, reserving resection for the time of progression or after the pandemic [5, 15, 19, 21, 24, 27–29, 39]. For patients on the transplant list, local ablative and regional therapies, such as transarterial chemoembolization (TACE), or transarterial radioembolization (TARE), can be more frequently used to bridge patients to ensure disease control while waiting for the transplant [16, 21, 28]. Some studies suggest postponement of surgical resection or liver transplantation in patients that respond well to the bridging treatment to a time when the surgery can be performed safely with sufficient resources [55].

Treatment of Intermediate-Stage HCC During the COVID-19 Pandemic

According to BCLC staging system, intermediate stage refers to multinodular, unresectable disease but with preserved liver function and good physical functional status [11–14, 49]. Conventionally, these set of patients benefit from radiologically administered locoregional therapies such as TACE or TARE [7, 9, 10, 12, 22, 55].

However, TACE being an interventional procedure exposes the clinician and the patients to risk of infection. TACE also requires multiple treatment sessions, hence more exposure with the pandemic stretching for more than 2 years [5, 20, 46]. However, in most of the guidelines adapted for the pandemic period, TACE remains the best treatment option for the intermediate disease [5, 22, 46]. It is also the alternative treatment for early disease where surgery is not possible due to restrictions brought about by the pandemic, where patients decline resection due to risks or as a bridging treatment in patients awaiting transplant, especially those within Milan but tumor size beyond ablation [55]. Stereotactic body radiotherapy should also be considered in this group of patients especially in the setting of the pandemic [21]. In case TACE services cannot readily be given to patients, systemic treatment or surveillance with regular imaging may be an alternative approach for intermediate-stage HCC [15].

Advanced Stage HCC

Advanced HCC is characterized by an Eastern Cooperative Oncology Group (ECOG) performance status of 1–2 and/or the presence of MVI or extrahepatic metastasis [7, 9, 41]. Tyrosine kinase inhibitors and immune checkpoint inhibitors are the mainstay treatment options for the advanced disease [15, 56, 57]. Some scholars proposed temporary use of systematic treatment at the height of the pandemic wave as an alternative to locoregional treatment basing it on previous studies that showed use of sorafenib as a decision of "treatment stage migration" showed good promising survival outcome [58, 59].

The main advantage of systemic therapy for the advanced stage is that it can be administered via prescription with telemedicine-based follow-up of the patient, hence reducing physician–patient contact [10, 22, 24]. Also, the drug can be delivered through courier to the patients' address which negates the need for the patient to come to the hospital for the medications [10, 22, 24]. However, clinicians should bear in mind some of the side effects of the medications such as immune checkpoint inhibitor linked immune pneumonia seen in 3–7% of the cases which needs to be distinguished from the COVID-19 [59–62]. There is also a bias towards orally administered systematic therapies over those requiring infusion to minimize contact and need for hospitalization.

Follow-up and Post-treatment Surveillance of HCC During the COVID-19 Pandemic

The curative therapy of HCC had been studied extensively but despite all that, recurrence rates have remained high. The 5-year disease-free survival (DFS) after curative therapy ranges from 19 to 81% [31, 32, 34, 47]. To ensure early identification and prompt therapy for recurrence lesions, closed surveillance protocol is necessary [7, 9, 22]. Most recurrence occurs within the first 2 years so a close surveillance is warranted in this period. The current National Comprehensive Cancer Network guidelines for surveillance after curative treatment for HCC recommend imaging every 3–6 months for 2 years, and then every 6–12 months thereafter. If initially elevated, AFP assessment is recommended every 3–6 months for 2 years and then every 6–12 months [41]. Ultrasound is the primary imaging of choice for surveillance [13, 22,

27, 34, 41]. It is readily available and cheap, has high specificity, and lacks radiation exposure. However, it shows significant examiner dependence and it is not very sensitive for lesions less than 20 mm. There have been attempts to improve these shortcomings by using sulfur-based contrast-enhanced ultrasound which increases sensitivity from 60 to 90% [63].

MDCT can also be used to survey for recurrent HCC. It shows more sensitivity compared with ultrasound (70 vs. 60%), high specificity (93%), and readily available. However, it costs more than USS and it exposes the patients to radiation. Contrast-enhanced MRI is the most sensitive imaging for surveillance of HCC especially for lesions less than 20 mm. It is also not associated with radiation exposure to the patients but is expensive and not readily available [32–34, 38, 47, 63]. Surveillance for recurrence in patients that had curative therapy was maintained during the COVID-19 pandemic to enable early identification of lesion for salvage therapy.

Post-pandemic Recovery

As the pandemic wears off, most of the global mandates put in place to reduce the spread of the disease are being lifted. This also presents a challenge of its own and the disciplines involved in management of HCC should expect the following:

1. Increased in the number of patients presenting to the clinic due to the backlog caused by the pandemic. This may necessitate the following measures:

(a) Triage to prioritize clinical appointments, investigations, and treatments to patients with more imminent needs like those with HCC that are eligible to curative treatment
(b) An extra clinic session because of the increased demand

2. The proportion of patients with more advanced HCC may increase due to the interruptions of the surveillance programs, delays, or interruptions in treatment.

Safety measures to prevent the spread of SARS-CoV-2 should be maintained in case of a return of the outbreak. As much as possible, triage to screen for chest symptoms, temperature, and contact tracing, if necessary, should still be implemented for every patient. Social distancing, including limiting the number of patients and accompanying individuals, in the clinical area should also be considered.

Conclusion and Lessons Learned

1. Potential role of artificial intelligence in patient management

   Artificial intelligence (AI) is a tool that has the potential to greatly enhance medical care [64, 65]. It implies the use of a computer to model intelligent behavior without human intervention. It emulates the decision-making process of humans via two major approaches. The first approach is the supervised machine learning, which aims to develop a predictive algorithm using regression or classification methods. The second approach is unsupervised machine learning, which allows computers to explore many unclassified data and to discover novel disease or treatment patterns [64, 65].

   The ability of AI to conduct mathematical modeling of how infections will spread may play a role in predicting future pandemics and this will assist public health agencies and governments in their reactions. This significantly reduces the uncertainty which may be responsible for societal unrest and individual anxiety. It will also assist in symptoms monitoring and advising the individual based on the symptoms they have. It may even be programmed to alert healthcare provider if something is wrong. AI could also track compliance in medications and it may serve as a reminder to the individual to take their medications on time [64, 65]. Contact tracing using locations and nearby phones could be useful if privacy is not violated.
2. Telemedicine and virtual tumor board meetings may be as effective as physical meetings

   One of the adaptive strategies adopted by most cancer specialist during the pandemic was the use of telemedicine to consult the patients to assess their symptoms and thereby stratify the patients based on the need to physically present in the hospital for further evaluation. This has reduced the risk of the spread of the COVID-19 infection and it ensures that patients with cancer still receive the best care available [66, 67].

   The use of virtual tumor board meetings is another important tool utilized by cancer specialist during the pandemic. It has enabled the different specialists involved in care of the patients to still share knowledge and treatment options without physically being in the same place [15].
3. Further research on blood-based marker for screening for HCC

The use of blood-based marker for screening of HCC has been researched over the years but the pandemic actually highlighted the need to do more because most of the acceptable screening tests require some degree of

closed contact. Alpha-fetoprotein lack both sensitivity and specificity in screening of HCC. There are some improvements with the use of GALAD panel but its sensitivity of 60–80% for early-stage detection can be improved [31, 38].

Author Contribution Akbulut S, Garzali IU, Hargura AS, and Aloun A wrote the manuscript; Yilmaz S and Akbulut S projected development and reviewed final version.

Declarations

Research Involving Humans and Animals No cell lines or human tissues were used for this manuscript.

Consent to Participate I consent to participate.

Consent for Publication I consent for publication.

Conflict of Interest The authors declare no competing interests.

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