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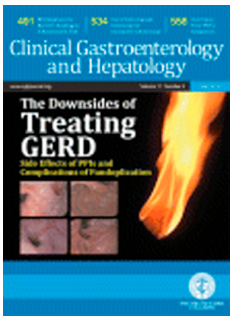

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Surveillance and Monitoring of Hepatocellular Carcinoma During the COVID-19 Pandemic

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Abbreviations: COVID-19, Coronavirus disease 2019; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; HBV, hepatitis B virus; CTP, Child-Turcotte-Pugh; NASH, non-alcoholic steatohepatitis; HCV, hepatitis C virus; MELD, Model for End Stage Liver Disease; RCT, randomized control trial; GALAD, gender, age, AFP-L3, AFP, and DCP; AFP-L3, lectin-reactive alpha-fetoprotein; DCP, des-gamma carboxyprothrombin; BCLC, Barcelona Clinic Liver Cancer; LT, liver transplantation; RETREAT, Risk estimation of tumor recurrence after liver transplantation; LRT, local regional therapy; SBRT, stereotactic body radiotherapy; TACE, trans-arterial chemoembolization; CMS, Centers for Medicare and Medicaid services; UNOS, United

Network for Organ Sharing; PD-L1, programmed death ligand 1; VEGF, vascular endothelial growth factor

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Conflicts of Interest: Neil Mehta has served on advisory boards for WAKO Diagnostics and has received institutional research funding from Wako Diagnostics, Glycotest, and Target Pharmasolutions. Neehar Parikh serves as a consultant for Bristol Myers-Squibb, Exact Sciences, Eli Lilly, and Freenome and has served on advisory boards for Genentech, Eisai, Bayer, Exelixis, and Wako Diagnostics. He has received institutional research funding from Bayer, Target Pharmasolutions, Exact Sciences, and Glycotest. R Katie Kelley has served on advisory boards for Agios, Astra Zeneca, Bristol Myers-Squibb, Genentech, and Gilead. She has received institutional research funding from Adaptimmune, Agios, Astra Zeneca, Bayer, Bristol Myers-Squibb, Eli Lilly, Exelixis, EMD Serono, Merck, Novartis, Partner Therapeutics, QED, and Taiho. Bilal Hameed has served on advisory boards for Surrozen and Gilead. He has received institutional research funding from Gilead, Intercept, Conatus, Genfit, and Salix/Valeant. Amit Singal has served on advisory boards or as a consultant for Wako Diagnostics, Glycotest, Exact Sciences, GRAIL, Bayer, Eisai, Genentech, Exelixis, Bristol Myers-Squibb, and TARGET Pharmasolutions.

Abstract

The Coronavirus disease 2019 (COVID-19) pandemic is expected to have a long-lasting impact on the approach to care for patients at risk for and with hepatocellular carcinoma (HCC) due to the risks from potential exposure and resource reallocation. The goal of this document is to provide recommendations on HCC surveillance and monitoring, including strategies to limit unnecessary exposure while continuing to provide high-quality care for patients. Publications and guidelines pertaining to the management of HCC during COVID-19 were reviewed for recommendations related to surveillance and monitoring practices, and any available guidance was referenced to support the authors' recommendations when applicable. Existing HCC risk stratification models should be utilized to prioritize imaging resources to those patients at highest risk of incident HCC and recurrence following therapy though surveillance can likely continue as before in settings where COVID-19 prevalence is low and adequate protections are in place. Waitlisted patients who will benefit from urgent LT should be prioritized for surveillance whereas it would be reasonable to extend surveillance interval by a short period in HCC patients with lower risk tumor features and those more than 2 years since their last treatment. For patients eligible for systemic therapy, the treatment regimen should be dictated by the risk of COVID-19 associated with route of administration, monitoring and treatment of adverse events, within the context of relative treatment efficacy.

Keywords: HCC; screening; alpha-fetoprotein (AFP); Coronavirus

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic continues to spread worldwide, with over 5.5 million confirmed cases and over 350,000 deaths. The surge of the pandemic has overwhelmed many health systems, leading to difficult decisions about clinical resource allocation. In response, many providers and health systems have restricted in-person encounters – including radiological imaging – and utilized telehealth visits to reduce exposure for both patients and providers. COVID-related risks may be especially relevant in patients with cirrhosis and hepatocellular carcinoma (HCC), for whom management often involves multiple interactions with the healthcare system (e.g. phlebotomy, radiological imaging, clinic visits, and HCC-directed treatments) but who may be more susceptible to severe COVID-related complications.

The COVID-19 pandemic is expected to have a long-lasting impact on the approach to care for all patients, including those with cirrhosis and HCC[1]. Many experts have predicted the need for social distancing and other precautions for at least the next 18-24 months. Even if COVID-19 transmission is drastically reduced or eliminated in the immediate future, recurrent outbreaks could occur over the next several years[2]. Therefore, the approach to HCC surveillance in patients with chronic hepatitis B (HBV) or cirrhosis, as well as HCC monitoring in those with HCC, with respect to resource allocation and disease management is not only a critical issue now but will potentially affect care delivery over several years. The goal of this document is to provide recommendations on HCC surveillance and monitoring during COVID-19, including strategies to limit unnecessary exposure while continuing to provide high-quality care for patients at risk for and with HCC. In settings where COVID-19 prevalence is low and

adequate protections are in place, surveillance and monitoring can likely continue as before though these recommendations can be considered as needed.

Methods

A targeted literature search was performed to identify PubMed-referenced publications pertaining to management of hepatocellular carcinoma in the setting of the COVID-19 pandemic as of 6 May 2020[1,3-6]. A manual search of professional society websites identified existing guidelines (Table 1) as of the same date. These publications and guidelines were reviewed for recommendations related to surveillance and monitoring practices, and any available guidance was referenced to support the authors' recommendations when applicable. The management considerations presented in this summary document were circulated for review to the multidisciplinary tumor board membership at the authors' respective institutions for input and represent a consensus opinion.

HCC surveillance in at-risk patients

Professional society guidelines recommend semi-annual HCC surveillance using abdominal ultrasound, with or without alpha-fetoprotein (AFP), in high-risk individuals[11,12]. This practice has been associated with increased early detection and improved survival in a large randomized controlled trial among HBV patients and several cohort studies in patients with cirrhosis[13,14]. However, during the outbreak of the COVID-19 pandemic, most health systems deferred elective imaging, including HCC surveillance. In patients with COVID-19 infection, HCC surveillance should be deferred until recovery. In addition to concerns about persistent risk of

COVID-19 exposure complicating re-opening of health systems, backlogs of patients waiting for deferred imaging may complicate availability of HCC surveillance imaging. Prioritizing HCC surveillance for those who derive the greatest benefit may be necessary; however, it may not be readily apparent how to best select these patients and the optimal surveillance strategies if ultrasound-based surveillance is not available.

HCC risk stratification models

Although surveillance is recommended in high-risk subgroups of patients with chronic HBV and all patients with cirrhosis, risk varies between patients and risk stratification models may be used to identify those with the highest HCC incidence. There are risk stratification models both among HBV patients, of which some have been validated in both Eastern and Western populations and cirrhosis patients, predominantly derived in Western populations (Table 2)[15]. To date, there has been limited validation of most models, so their clinical utility in routine practice has remained limited. However, in a restricted resource environment, components of these stratification systems could be used to identify patients who can be prioritized for surveillance and those who may be deferred.

Older age and male gender are consistent components of HCC risk stratification models. Child-Turcotte-Pugh (CTP) score and presence of portal hypertension are other important risk factors for HCC; however, this must be balanced with likely increased susceptibility to COVID-19 in those with advanced liver dysfunction. Finally, liver disease etiology is a consistent risk factor, with active viremia associated with a 3-6% annual risk, whereas patients with non-alcoholic steatohepatitis (NASH), alcohol-related liver disease, or hepatitis C (HCV) cirrhosis after viral

cure have a lower annual risk of 1-2%[21]. Patients with combinations of high risk features may be considered as the highest priority for surveillance receipt, whereas surveillance may be deferred in those with one or no risk factors.

HCC surveillance in selected populations

Continued careful patient selection is critical, including not ordering HCC surveillance in patients unlikely to benefit. Patients with CTP C cirrhosis who are not transplant eligible are not recommended to undergo surveillance because of the competing risk of liver-related mortality. Similarly, patients with other significant comorbidities (e.g. cardiovascular disease, malignancies) that limit life expectancy or treatment eligibility should not undergo surveillance. Surveillance should also not be performed in certain subgroups at lower risk, e.g. HCV or NASH patients in absence of cirrhosis given marginal risk-benefit ratio[21,22]. Preventing over-surveillance in populations unlikely to benefit is a practical way to minimize harms of surveillance, including possible COVID-19 exposure.

On the other hand, while some transplant centers have suspended or limited transplants to those with high MELD scores, the listed population could be considered a priority for surveillance receipt. Early detection (e.g. within Milan criteria) is critical in this population to prevent waitlist dropout and timely identification of HCC lesions allows patients to accrue waiting time with MELD exception. Additionally, surveillance can provide other information relevant to transplant decision making, such as development of portal vein thrombosis. Therefore, while some deferments of HCC surveillance may be necessary in the setting of a

local COVID-19 outbreak, listed patients should likely be prioritized to receive surveillance as available.

Timing of HCC surveillance in at-risk patients

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. Recommendations to perform semi-annual surveillance were initially based on tumor doubling time from older studies demonstrating tumor doubling times of 4-6 months. These data have since been replicated in contemporary cohort studies, although a meta-analysis suggests potential shorter doubling times in HBV-predominant populations[23,24]. A large randomized control trial (RCT) from France demonstrated quarterly surveillance does not improve early HCC detection compared to semi-annual[25]. Although there is not a similar RCT evaluating longer intervals, retrospective cohort studies have shown semi-annual surveillance results in increased early detection and improved survival compared to annual surveillance, after adjusting for lead time bias[26]. However, the difference in survival benefit between the two intervals appears small, and both significantly improve survival compared to no surveillance. There are also no data comparing semi-annual surveillance to intermediate length surveillance intervals between 8 and 10 months. Deferring HCC surveillance over short periods of time, as needed, is likely acceptable in light of an annual HCC incidence of 2-3%, suggesting ~98% of patients will not develop HCC over any single surveillance interval.

HCC surveillance tests in at-risk patients

If ultrasound-based surveillance is not possible for extended periods of time, blood-based biomarkers may be considered as an alternative strategy. Ultrasound with or without AFP achieve a sensitivity of ~63% for early HCC detection when used in combination, although performance may be lower in patients with NASH given increased concerns about poor ultrasound visualization[27,28]. Although ultrasound is readily available in most areas, logistics of ultrasound-based surveillance, including need for a separate appointment, is a common patient-reported barrier to surveillance completion[29]. This issue may be increasingly problematic in times where social distancing is recommended and patients are concerned about in-person visits. Given potential concerns about lack of social distancing between the ultrasound operator and patient, MRI-based surveillance could also be considered though this strategy is limited by cost-effectiveness when applied to broad populations of cirrhosis patients.

An alternative strategy which could mitigate some issues is blood-based biomarkers, as these can be done the same day as a clinic visit without a separate appointment. Although several serum-based biomarkers have been proposed, none except AFP have undergone phase III or IV validation in cohort studies[30]. AFP has insufficient sensitivity and specificity to be used alone, although data suggest diagnostic performance is higher in patients with non-viral cirrhosis or HCV patients after virologic cure[31,32]. Further, using longitudinal changes in AFP can increase accuracy for early HCC detection than single-threshold measurement at a cut-off of 20 ng/mL[33]. Given similar concerns about insufficient accuracy for other single biomarkers, there has been increasing interest in biomarker panels. The best evaluated to date is GALAD, which combines gender, age, and three biomarkers – AFP, AFP-L3, and DCP. The panel has demonstrated sensitivities of 60-80% for early stage detection in large multi-national case-

control studies, including recent data among NASH patients[34,35]. GALAD has shown superior performance to the component biomarkers, in part related to inclusion of gender and age in the biomarker algorithm. Although this performance needs to be validated in cohort studies prior to routine use in clinical practice, blood-based biomarkers such as GALAD, AFP-adjusted algorithms, or longitudinal AFP may be a reasonable alternative if ultrasound-based surveillance cannot be easily performed for extended periods of time. Although unknown, surveillance intervals would likely be unchanged from ultrasound-based surveillance as they are based on tumor doubling times and not test performance characteristics.

Monitoring patients after potentially curative HCC therapy

HCC patients with Barcelona Clinic Liver Cancer (BCLC) stage 0/A (single lesion or 2-3 lesions, each <3cm) are typically treated with curative treatments including resection, ablation, or liver transplantation (LT); however, there is a persistent risk of recurrence after each treatment[36-39]. Given that long-term survival can be achieved with early detection of HCC recurrence[40,41], ongoing HCC surveillance after curative therapy is recommended. Given higher HCC risk after curative therapy than in those with cirrhosis, surveillance is typically performed using cross-sectional imaging with multiphase abdominal CT or contrast-enhanced MRI with or without non-contrast CT chest. After resection (or ablation), less than 25% of recurrences are extra-hepatic[42] so the chest CT can likely be forgone outside of situations such as rising AFP with negative abdominal imaging – particularly if this requires a separate visit and there is limited radiologic capacity.

Timing of HCC surveillance after potentially curative HCC treatment

Similar to HCC surveillance among at-risk patients, surveillance after curative therapies for HCC has been associated with early stage detection and improved survival[43]. While recurrence can be seen for up to 10 years following resection or LT[36], most recurrences occur within the first 2 years[44,45] so surveillance should be prioritized during this period. To determine appropriate post-treatment surveillance intervals, an estimation of individual recurrence risk should be undertaken. Multiple HCC recurrence risk scores that consider pathological analysis of the surgical specimen along with biomarkers (e.g. AFP) have been established in the LT[44,46,47] and resection population[48-50], although few have been validated. The RETREAT score[44,51] is one validated risk stratification model that can be used to identify patients at highest risk of post-LT recurrence and who should be prioritized for surveillance in time of limited radiologic capacity. Patients with a RETREAT score of 0 have a <3% recurrence risk and likely do not benefit from surveillance. Likewise those with RETREAT scores of 1-3 can likely safely defer surveillance, particularly if beyond 2 years after LT. In contrast, those with RETREAT scores of ≥4 should likely continue at least semi-annual surveillance until year 5 (Table 3)[44]. In contrast, recurrence after resection and ablation is very common and early detection is critical given the possibility of salvage transplant for those detected within Milan criteria[52,53]. Therefore, under normal circumstances, post-resection or ablation surveillance should be performed approximately every 3-4 months for the first 2 years followed by every 4-6 months for years 2-5. In periods of limited radiologic capacity, it would be reasonable to extend each recommend interval by a short period (e.g. extending 2-3 months), particularly in those with

lower risk features (e.g. absence of poorly differentiated histology or microvascular invasion) and those more than 2 years beyond their treatment (Table 3).

Monitoring HCC patients undergoing local-regional treatment

There is consensus that HCC patients should continue to receive local-regional therapy (LRT) during the COVID-19 pandemic, with choice of therapy discussed in a multidisciplinary format[54]. Risk of potential exposure versus presumed benefit of treatment should be discussed, with a lower threshold to delay palliative LRT procedures in elderly patients and in those with comorbidities[4]. COVID-19 testing should be performed approximately 48-72 hours prior to administering LRT. Factors specific to COVID-19 include local infection prevalence, infection risk after treatment, need for inpatient stay after LRT, use of general anesthesia, interventional radiology capacity, and hospital resources among others. For example, external stereotactic body radiotherapy (SBRT) typically involves multiple treatment sessions over several days though does not require post-procedure admission. Patients scheduled for Y-90 radioembolization commonly undergo angiography 1–2 weeks prior to treatment to evaluate for significant shunting that would make patients ineligible for Y-90 therapy. However, lung shunt fraction is negligible in early-stage patients receiving segmental Y-90 so this step may be eliminated[55] which would reduce health care utilization and potential COVID-19 exposure. There is concern for serious COVID-19 infection in those receiving conventional TACE (cTACE with cytotoxic agents) because of systemic absorption with increased myelosuppression and therefore ILCA recommends other forms of LRT over cTACE (e.g. bland embolization, drug-

eluting bead (DEB)-TACE, Y-90)[10]. Finally, consideration for earlier transition to systemic therapy could be considered in locally advanced HCC patients[56].

Timing of HCC surveillance to assess treatment response after LRT

There is limited guidance about timing and follow up of post-LRT surveillance with wide variation in interventional radiology practices[11,57,58]. Follow-up cross-sectional imaging should be performed approximately 4-6 weeks after TACE or ablation to assess response and determine need for repeat treatment[59] (Table 3). In contrast, arterial enhancement and washout can persist for several months after radiation-based treatment (SBRT, Y-90), complicating radiologic interpretation within the first couple months[60,61]. Therefore, especially during the COVID-19 pandemic, imaging after Y-90 or SBRT can likely be delayed and performed ~3-4 months after therapy (Table 3). AFP can also potentially be used as a marker for response to LRT with imaging being delayed in patients with a significant drop in AFP from baseline (e.g. >50%)[62]. Patients without viable disease after any form of LRT are recommended to undergo follow-up imaging every 3–4 months[59], although this also may be delayed in light of COVID-19 exposure risk, particularly for those with durable responses. In patients with worsening liver dysfunction, declining performance status, or other features that would preclude repeat treatment, imaging to assess response may also be deferred unless required for other reasons (e.g. transplant eligibility).

HCC monitoring in patients listed for liver transplant

Currently in the United States, HCC patients within Milan criteria currently receive MELD exception after a mandatory 6 month wait to facilitate LT. Centers for Medicare and Medicaid services (CMS) guidelines regarding surgery during the COVID-19 pandemics have categorized "transplant" as the highest priority[63]. LT at some centers has been limited to the sickest (e.g., acute liver failure, MELD $\geq$25), while less urgent cases are postponed because of limited resources with many living donor liver transplant programs being suspended. United Network of Organ Sharing (UNOS) recently announced policies to address changes during the COVID-19 pandemic to ensure that HCC patients will not be disadvantaged due to the national public health emergency[64]. The policy now authorizes programs to "carry forward" clinical data and imaging from prior exception petitions, such as with HCC MELD exceptions, if obtaining updated data is not possible. However, it is important to obtain preoperative imaging at admission for LT if not done within the prior three months to ensure conventional LT criteria (i.e. Milan) are still met.

In this climate, it is important to be able to risk stratify patients with HCC with moderate to high risk of waitlist dropout who will benefit from urgent LT during this period versus those with more indolent disease and a lower risk of dropout. Specifically, patients with a combination of favorable tumor characteristics (e.g. single lesion <3 cm, AFP $\leq$20 ng/mL, complete response to LRT) and liver function (e.g. CTP A cirrhosis and MELD score $\leq$13-15) appear to have a low-risk of waitlist dropout[65,66]. It would be appropriate to delay LT in such low-risk patients given lack of urgency and decreased LT survival benefit[66] and consider temporary inactivation.

Monitoring HCC patients undergoing systemic therapy

There are now multiple systemic therapies available for patients with advanced stages of HCC. In the first-line setting, treatment options include the multikinase inhibitors, sorafenib[67,68] and lenvatinib[69]. The combination of atezolizumab, a monoclonal antibody targeting the programmed death ligand 1 (PD-L1), combined with bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF), has become a new standard for first-line therapy based upon survival improvement over sorafenib[70]. After progression on first-line therapy, treatment options depend on local regulatory approvals; in the U.S., approved therapies include the multikinase inhibitors, regorafenib[71] and cabozantinib[72]; a VEGF monoclonal antibody, ramucirumab[73]; and the immune checkpoint inhibitors, nivolumab[74] and pembrolizumab[75]. Without established biomarkers beyond AFP, the choice of treatments in first- and later-line therapy depends upon individual patient prognostic factors and an estimation of risk of adverse events from each therapeutic option. During the COVID-19 pandemic, local infection rates may influence systemic therapy risk assessment, monitoring capabilities, and choice of therapy.

The type of systemic therapy impacts the frequency and nature of monitoring required. For multikinase inhibitors with daily oral dosing, safety monitoring includes frequent blood pressure measurement, skin inspection particularly of palms and soles for evolving palmar-plantar erythrodysesthesia findings, and laboratory testing of electrolytes and liver function. Rare but serious complications including hemorrhagic events and venous or arterial thromboembolism occur in a minority of patients[67-69,71,72]. In patients treated with immune checkpoint inhibitor-based regimens, safety monitoring by laboratory testing and clinical

encounters generally occurs at the same frequency as infusions, at intervals ranging from two to six weeks depending on agent and dosing regimen[74-76]. Safety monitoring on immune checkpoint inhibitors requires vigilance for immune-related adverse events, which can range from more common events of mild rashes and arthralgias, to rare but potentially life-threatening events such as encephalitis, hypophysitis, myocarditis, pneumonitis, hepatitis, and colitis[77]. Immune-mediated adverse events can evolve and progress rapidly and may require high doses of steroids, other immunosuppressive therapies, and hospitalization in severe cases.

In regions with high rates of COVID-19 transmission, safety monitoring via telemedicine may be an option for patients with access to technology[3,4,9]. For patients treated with multikinase inhibitors, telemedicine monitoring requires patient or caregiver access and training on sphygmomanometry. Digital photographs of palms, soles, and any other areas of skin change can be uploaded to an electronic medical record for provider review. Laboratory tests can be performed at a local laboratory or, in some cases, via mobile phlebotomy, to minimize exposures to patient and health system. In patients treated with immune checkpoint inhibitors, regular visits to an infusion center remain necessary, along with laboratory monitoring. Patients and caregivers require education on the risks and warning symptoms of immune-related adverse events which can require urgent medical evaluation[77].

Choice of systemic therapy in advanced HCC

Regional COVID-19 exposure risk may impact choice of systemic therapy in advanced HCC based upon availability of local resources (e.g. infusion center, endoscopy, clinical trials) and risk of regimen-specific toxicities (e.g. immune-related adverse events which may require

high doses of corticosteroids). Testing for active COVID-19 infection should be considered prior to initiation of therapies according to local institutional practice at the time of initiation, particularly for regimens with risk for immunosuppression[3,8]. When considering first-line therapy options, the combination regimen of atezolizumab plus bevacizumab requires infusion of atezolizumab at three week intervals, along with a screening endoscopy within six months prior to treatment owing to risk of variceal hemorrhage associated with bevacizumab in prior phase 2 studies[70,78,79]. If endoscopy and/or infusion center services are not available in a pandemic setting, an alternate first line agent such as lenvatinib or sorafenib may offer a more favorable ratio of benefit to risk (Table 4). In the second-line and later treatment setting, the median durations of progression-free survival are longer, while rates of primary progressive disease are lower, for the multikinase inhibitors, regorafenib[71] and cabozantinib[72], compared to monotherapy with immune checkpoint inhibitors[74,75]. These efficacy parameters along with oral dosing without infusion center requirement likewise may favor the choice of regorafenib or cabozantinib as second-line therapy in the context of a pandemic. Immune checkpoint inhibitor therapies, particularly in combinations such as the regimen of nivolumab plus ipilimumab[76], also confer a risk of immune-related complications requiring corticosteroid or other immunosuppression (Table 4), which may further increase COVID-19 transmission risk and severity. In regions with high rates of COVID-19 infection, an alternate regimen may be preferred.

Timing of HCC surveillance to assess treatment response with systemic therapy

For advanced HCC patients treated with systemic therapies, radiographic response is assessed using cross-sectional imaging of the chest, abdomen, and pelvis, usually within three months after treatment initiation[81]. Though radiographic response is the gold standard for assessment of progression, continuation of treatment until symptomatic progression is an accepted practice for patients treated with multikinase inhibitors[68,69,71,72]. In regions with high community COVID-19 transmission, extended imaging intervals may be appropriate in patients without symptomatic progression on systemic therapy[10]. Beyond radiographic and clinical response assessment, serum AFP levels may also be a useful adjunct. Approximately 60-80% of patients with advanced HCC have elevated AFP at start of systemic therapy[82]. In patients with elevated AFP of at least 1.5 times upper limit of normal or 20 ng/mL at start of treatment, changes in AFP on treatment have shown association with outcomes on multiple types of systemic therapies, including sorafenib, cabozantinib, and ramucirumab[82-85]. Stabilization or decline in serum AFP on treatment, commonly defined as a decrease of at least 20%, has been shown to correlate with prolonged progression-free and overall survival, while increases in AFP correlate with poor outcomes. Though optimal thresholds of AFP response and progression require further validation, serum AFP kinetics offer an additional tool for response assessment (Figure 1) during the COVID-19 pandemic, when imaging may not be readily available and could confer additional risk of viral exposure.

Conclusions

The COVID-19 pandemic has dramatically changed the delivery of health care worldwide. The resource intensive management of patients with cirrhosis and HCC is

particularly vulnerable to decreased health care resources during a pandemic. A principle of maximizing the risk-benefit ratio should be taken for the surveillance of HCC and monitoring of patients who have received therapies for HCC. Prioritizing imaging resources to those patients at highest risk of incident HCC and recurrence following therapy, while prioritizing those patients who are eligible for an imminent LT, is a judicious strategy to risk stratifying these patients. For patients eligible for systemic therapy, the landscape is changing rapidly, however the treatment regimen should be dictated by the risk of COVID-19 associated with: route of administration, monitoring and treatment of adverse events, within the context of relative efficacy for the treatment of HCC. These principles hold not only during times of active local transmission, but also in the post-pandemic period when prioritizing the backlog of patients in whom care was deferred due to limited health care resources. Patients at risk for and with HCC are among the highest acuity patients as a whole, but allocating resources to those with the highest likelihood of benefit while minimizing exposure risk to COVID-19 is a prudent approach in a limited resource environment.

Figure Legend

Figure 1. Suggested algorithm for incorporation of serum AFP in systemic therapy response assessment during COVID-19 pandemic

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Table 2. HCC Risk Stratification Models

Author, year	Components	Derivation	External Validation	Link
Ioannou, 2019[16]	Age, gender, diabetes, body mass index, platelet count, serum albumin and aspartate aminotransferase to alanine aminotransferase ratio	23,234 patients with **NASH or alcohol related cirrhosis**; 1,237 developed HCC C-statistic: 0.75-0.76	None	https://www.journal-of-hepatology.eu/article/S0168-8278(19)30291-0/fulltext
Sharma, 2019[17]	Age, gender, etiology, platelet count	2,079 patients with **mixed etiologies of cirrhosis**, 226 developed HCC C-statistic: 0.76	1,144 patients with **mixed etiologies of cirrhosis**, 107 developed HCC C-statistic: 0.77	https://www.journal-of-hepatology.eu/article/S0168-8278(17)32248-1/fulltext
Papatheodoridis, 2016[18]	Age, gender, platelet count	1,325 patients with **chronic hepatitis B** on entecavir/tenofovir, 51 developed HCC C-statistic: 0.82	490 patients with **chronic hepatitis B** on etecavir/tenofovir, 34 developed HCC C-statistic: 0.82	https://www.journal-of-hepatology.eu/article/S0168-8278(15)00795-3/fulltext
Flemming, 2014[19]	Age, race, diabetes, etiology, gender, Child-Pugh score	34,392 patients with **mixed etiologies of cirrhosis,** 1,960 developed HCC C-statistic: 0.704	426 patients with **hepatitis C cirrhosis**, 29 developed HCC C-statistic: Not reported	https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.28832
Yang, 2011[20]	Sex, age, alanine aminotransferase, hepatitis B e antigen status, hepatitis B DNA	3,584 patients with **chronic hepatitis B**, 131 developed HCC	1,505 patients with **chronic hepatitis B**, 111 developed HCC C-statistic (10 year risk): 0.77	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70077-8/fulltext

Table 3. Approach to surveillance after HCC surgical and local-regional treatments under normal conditions and during COVID-19

HCC Treatment Received	Surveillance Recommendations Under Normal Conditions	Surveillance Recommendations During COVID-19
Liver Transplantation 5-year recurrence risk Very low <5% (e.g. RETREAT 0*) Low (5-15%) Moderate (15-30%) High (>30%) (e.g. RETREAT ≥5*)	No surveillance Cross-sectional imaging of chest/abdomen + AFP Every 6 months for 2 years Every 6 months for 5 years Every 3-4 months for 2 years then every 6 months from years 2-5	No surveillance Cross-sectional imaging of chest/abdomen + AFP Every 6-8 months for 2 years Every 6-8 months for 5 years Every 3-6 months for 2 years then every 6-8 months from years 2-5
Resection	Cross-sectional imaging of abdomen + AFP every 3-4 months for 2 years then every 6 months from years 2-5	Cross-sectional imaging of abdomen + AFP every 3-6 months for 2 years then every 6-8 months from years 2-5
Ablation*	Cross-sectional imaging of abdomen + AFP every 3 months for 2 years then every 4-6 months from years 2-5	Cross-sectional imaging of abdomen + AFP every 3-4 months for 2 years then every 4-8 months from years 2-5
TACE*	Cross-sectional imaging of abdomen + AFP 4 weeks after TACE then every 3 months (if no recurrent disease)	Cross-sectional imaging of abdomen + AFP 4-8 weeks after TACE then every 3-4 months (if no recurrent disease)
Y90 or SBRT*	Cross-sectional imaging of abdomen + AFP 4-8 weeks after Y90 or SBRT then every 3 months (if no recurrent disease)	Cross-sectional imaging of abdomen + AFP 2-4 months after Y90 or SBRT then every 3-4 months (if no recurrent disease)

* The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score[44,51] incorporates 3 variables that independently predict HCC recurrence: microvascular invasion (MVI), AFP at LT, and the sum of the largest viable tumor diameter and number of viable tumors on explant.

**For HCC patients listed for liver transplant, UNOS requires cross-sectional imaging of abdomen + AFP at least every 3 months to maintain priority listing under normal conditions. During COVID-19, especially in patients at low risk for waitlist dropout, could consider extending this interval up to every 4-5 months.

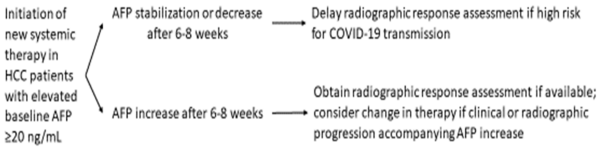
Table 1. Selected Professional Society Guidelines and Position Statements on Management of HCC during COVID-19 Pandemic

Professional Society	Guideline Reference	Description
American Association for Study of Liver Disease (AASLD)	https://www.aasld.org/about-aasld/covid-19-resources	COVID-19 Resources
American Society of Clinical Oncology (ASCO)	https://www.asco.org/asco-coronavirus-information/provider-practice-preparedness-covid-19	Ethics and Resource Scarcity: ASCO Recommendations for the Oncology Community During the COVID-19 Pandemic[7,8]
European Association for Study of the Liver (EASL)	https://easl.eu/covid-19-and-the-liver/	Care of Patients with Liver Disease during the COVID-19 Pandemic: EASL-ESCMID Position Paper[3]
European Society of Medical Oncology (ESMO)	https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gastrointestinal-cancers-hepatocellular-carcinoma-hcc-in-the-covid-19-era	ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: HCC[9]
International Liver Cancer Association (ILCA)	https://ilca-online.org/management-of-hcc-during-covid-19-ilca-guidance/	Management of HCC During COVID-19: ILCA Guidance[10]
National Comprehensive Cancer Network (NCCN)	https://www.nccn.org/covid-19/	Coronavirus Disease 2019 (COVID-19) Resources for the Cancer Care Community

Table 4. Serious adverse event rates for systemic therapies and strategies to minimize COVID-19 exposure risk during a pandemic

Regimen	All-Cause Serious Adverse Events	Corticosteroid Requirement	Strategies to minimize COVID-19 exposure risk
First-Line Options			Consider alternate therapy in patients at risk for varices who require endoscopic surveillance; consider use of Baveno VI criteria for variceal assessment if elastography available[3,80]
Atezolizumab plus bevacizumab[70]	38.0%	NR	
Lenvatinib[69]	43%	NA	Consider remote safety monitoring: • Telemedicine visits • Home blood pressure measurement • Local laboratory or mobile phlebotomy service • Digital photography for hand/foot skin lesions
Sorafenib[68]	52%	NA	
Second- and Later-Line Options			
Regorafenib[71]	44%	NA	
Cabozantinib[72]	50%	NA	
Ramucirumab[73]	35%	NA	Consider multikinase inhibitor if infusion center not accessible
Nivolumab plus ipilimumab[76]	22%*	51%	Consider nivolumab monotherapy or multikinase inhibitor to minimize risk of immunosuppression and infection
Nivolumab[74]	7%*	NR	Can treat with extended dosing interval of 4 weeks to reduce infusion center visit frequency if clinically appropriate; consider multikinase inhibitor if infusion center not accessible
Pembrolizumab[75]	NR	8.2%	Can treat with extended dosing interval of 6 weeks to reduce infusion center visit frequency if clinically appropriate; consider multikinase inhibitor if infusion center not accessible

Key: NA, not applicable; NR, not reported; *, reported only the rates of treatment-related rather than all-cause serious adverse events.


Initiation of new systemic therapy in HCC patients with elevated baseline AFP ≥20 ng/mL
AFP stabilization or decrease after 6-8 weeks
Delay radiographic response assessment if high risk for COVID-19 transmission
AFP increase after 6-8 weeks
Obtain radiographic response assessment if available; consider change in therapy if clinical or radiographic progression accompanying AFP increase