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Special Report

Treatment of hepatocellular carcinoma during the COVID-19 outbreak: The Working Group report of JAMTT-HCC

Masatoshi Kudo,[1] Masayuki Kurosaki,[2] Masafumi Ikeda,[3] Hiroshi Aikata,[4] Atsushi Hiraoka,[5] Takuji Torimura[6] and Naoya Sakamoto[7]

[1]Department of Gastroenterology and Hepatology, Faculty of Medicine, Kindai University, [2]Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, [3]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, [4]Department of Gastroenterology and Metabolism, Graduate School of Biomedical and Health Science, Hiroshima University, [5]Department of Gastroenterology, Ehime Prefectural Central Hospital, [6]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, and [7]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido University

This contingency guide was formulated on the premise that delivering standard treatment for hepatocellular carcinoma (HCC) has come under strain due to the coronavirus (COVID-19) pandemic. Measures required are likely to vary largely across regions and individual institutions, depending on the level of the strain imposed by the pandemic (e.g., number of inpatients infected with COVID-19 and the availability of resources, including personal protective equipment and inpatient beds). In addition, models suggest that the second and third waves of COVID-19 will occur before effective vaccines and medicines become widely available in Japan (expected time, 2–3 years). This guide should serve as a good reference for best practices in the management of HCC, which is in light of the possible risk of impending collapse of the healthcare system due to a surge in COVID-19 infections.

Key words: COVID-19, hepatocellular carcinoma, JAMTT-HCC | liver dysfunction | systemic therapy | up-to-seven criteria

BACKGROUND

AS OF JULY 8, 2020, the number of patients worldwide with novel coronavirus (COVID-19) infection stands at 11,669,259, with 539,906 deaths, across 216 countries,[1] including 20,174 infected patients, with 980 deaths, in Japan.[2] Among patients with COVID-19 in Japan, 19,193 have been hospitalized, with 17,331 being discharged and 35 with a fatal condition; moreover, the number of infected patients in Japan is still rising.[2] Although the number of the most critically ill patients with COVID-19 who require mechanical ventilation has been decreasing since the Japanese government declared a nationwide state of emergency on April 7, 2020, another COVID-19 surge is highly likely when economic activities resume with the lift of the state of emergency on May 25, 2020. In addition, in the long term, the nation should be prepared for the second and third waves of COVID-19 as restrictions on entry from Asia, Europe and the United States are lifted in stages.

Correspondence: Masatoshi Kudo, Department of Gastroenterology and Hepatology, Faculty of Medicine, Kindai University, 377-2, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. Email: m-kudo@med.kindai.ac.jp
Naoya Sakamoto, Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido University, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan. Email: sakamoto@med.hokudai.ac.jp
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An explosive surge of infections in Europe and the United States has put an enormous strain on their healthcare systems, burdening healthcare professionals in some countries with the unbearable decision of choosing patients who should and should not be saved. In these countries, maintaining the healthcare system has become extremely difficult, making it impossible to deliver standard treatment for other patients, even those with serious conditions (e.g., cancer and cerebrovascular/cardiovascular disease), in some regions and some institutions.

Information about cancer treatment during the COVID-19 pandemic has been given to patients, and clinical practice guidance has been given to healthcare professionals, by relevant societies overseas and in Japan, including the American Society of Clinical Oncology (ASCO),[3] European Society for Medical Oncology (ESMO),[4] National Institute for Health and Care Excellence (NICE)[5] and the Japanese Society of Medical Oncology (JSMO).[6] Similarly, clinical practice guidance for liver diseases and liver cancer has been released to healthcare professionals by the International Liver Cancer Association (ILCA),[7,8] the European Association for the Study of the Liver (EASL)[9] and the American Association for the Study of Liver Diseases (AASLD)[10] (Table 1).

The policy formulated by the ILCA recommends appropriate use of telemedicine to reduce the frequency of hospital visits and avoid hospital admission, selecting patients most likely to benefit from therapies (e.g., surgical resection, radiofrequency ablation [RFA] and transarterial chemoembolization [TACE]) and postponing treatments for others.[7,8] These guidelines also recommend using the up-to-seven criteria in selecting patients for TACE, as well as the use of alternative treatments. In addition, the frequency of visits for the infusion of immune checkpoint inhibitors should be reduced, so that patients with liver cancer can avoid the risk of COVID-19 associated with hospital visits. Recommendations in the EASL position paper are stronger than those of the ILCA, such as postponing locoregional therapies (e.g., RFA and TACE) and temporarily discontinuing immune checkpoint inhibitor therapy.[9]

Because of the strain on the Japanese healthcare system due to the COVID-19 pandemic, the Working Group of the Japan Association of Molecular Targeted Therapy for Hepatocellular Carcinoma (JAMTT-HCC) was established to develop guidance for the clinical management of HCC (a modified version of the existing guidelines[11]), which can be used in the most challenging situations. The recommendations made by the JAMTT-HCC were based on the above-mentioned ILCA and EASL guidelines. This manuscript explains the Working Group Report of the JAMTT-HCC.[12]

RISKS OF COVID-19 AND OF SERIOUS ILLNESS FROM COVID-19 IN PATIENTS WITH CANCER

PATIENTS WITH CANCER have been reported to be at higher risk of COVID-19 infection,[13] and COVID-19 infection has been found to increase mortality rates in patients with cancer[14,15] (Table 2). For example, a Chinese group reported that, of 1590 individuals infected with COVID-19, 18 (1.1%) were cancer survivors or patients with cancer, including five with lung cancer, four with colon cancer, two with breast cancer and two with bladder cancer.[15] The risk of mortality was higher and the time to death was shorter (hazard ratio, 3.56; 95% confidence interval [CI], 1.65–7.69) in cancer survivors and patients with cancer than in individuals without cancer.[15]

Risk factors identified for COVID-19 infection in patients with cancer include the last anticancer treatment within 14 days before diagnosis of COVID-19 infection and advanced age (e.g., ≥65 years).[14,16] Of 1276 patients at three hospitals in Wuhan, China, with confirmed COVID-19, 28 (2.2%) had cancer, including seven with lung cancer, four with esophageal cancer, three with breast cancer, two with laryngeal cancer, two with HCC and two with prostate cancer, with all 28 patients with COVID-19 and cancer having a history of anticancer treatment.[16] The risk of severe events (e.g., admission to the intensive care unit, use of mechanical ventilation and death) was significantly higher in those who did than did not receive their last anticancer treatment within 14 days before the diagnosis of COVID-19 (hazard ratio, 4.079; 95% CI, 1.498–19.748; $P=0.010$).[16] Moreover, the risk of COVID-19 infection was about twofold higher in patients with than without cancer (odds ratio, 2.31; 95% CI, 1.89–3.02). The incidence of COVID-19 was also higher in patients with lung cancer aged ≥60 than < 60 years (4.3% vs. 1.8%).[16] Another study of 1524 patients with COVID-19 in Wuhan, China, during the same period, found that 12 (0.79%) had cancer, including seven with lung cancer and one each with rectal, colon, pancreatic, breast and urothelial cancer.[14] Although studies to date have included few patients with COVID-19 with HCC, the limited data available highlight the potential risk of COVID-19 infection in patients with cancer.

HCC is often associated with liver cirrhosis, suggesting that impaired immunity will increase the risks of COVID-19 infection and of serious illness from COVID-19. This likely prompted both the ILCA and EASL to release guidance on clinical practice for HCC in situations where the healthcare system comes under strain.

We would like to believe that Japan could continue to avoid an explosive surge of COVID-19 infection and the

Table 1 ILCA Guidance and EASL Position Paper on HCC treatment during the COVID-19 pandemic

	ILCA[7,8]	EASL[9]
General matters	• Reduce hospital visits and use telemedicine to prevent hospital-acquired COVID-19 infection • Where visits cannot be avoided, use personal protective equipment in line with national guidance • When bridging therapy or active monitoring is offered in place of potentially curative interventions, patients should be closely monitored, including with imaging methods and measurement of AFP, to reduce their risk of progressing beyond criteria for transplant, resection or RFA • Where feasible, cancer therapy should be offered in a 'COVID-free' institution	• Care should be maintained according to guidelines but consider minimal exposure to medical staff by telemedicine and telephone contacts wherever possible/required to avoid admission to hospital • Early admission is recommended for patients with COVID-19
Surgical resection	• Select patients with lower risk of decompensation • Select patients without comorbidities that increase the risk of severe COVID-19 **Alternative/holding therapy: ablation if anesthetic capacity allows, Bridging TA(C)E, SBRT, bridging systemic therapy, active monitoring with imaging**	NA
Transplant	• Temporary suspension of elective living donor transplantation may be considered to protect both the potential donor and recipient • Consider delayed transplant in patients on the transplant list with complete response to bridging therapy; however, the risk of delaying transplant in patients with viable tumors and/or significant liver dysfunction should be discussed with the patient **Alternative/holding therapy: ablation if anesthetic capacity allows, bridging TA(C)E, bridging SBRT, bridging systemic therapy (excluding checkpoint inhibition given the risk of rejection), active monitoring with imaging**	• Listing for transplantation should be restricted to patients with poor short-term prognosis, including those with acute/acute-on-chronic liver failure, high MELD scores (including exceptional MELDs), and HCC at the upper limits of the Milan criteria, as transplantation activities/organ donations will likely be reduced in many countries and areas • Reduce the in-hospital liver transplant evaluation program to that which is strictly necessary to shorten in-hospital stay and reduce the number of consultations in other departments/clinics. Ophthalmologic, dermatologic, dental and neurologic consultations can be performed in local outpatient settings Before transplantation • Donors and recipients should be routinely tested for SARS-CoV-2 before transplantation • Consent for diagnostic and therapeutic procedures related to transplantation should include the potential risk of nosocomial COVID-19 • Living-donor transplantations should be considered on a case-by-case basis After transplantation • Emphasis on the importance of vaccination for *Streptococcus pneumoniae* and influenza • Stable patients should be tested at local laboratories, including measurement of drug levels • Immunosuppressive therapy should not be reduced, except under special circumstances after consultation with a specialist • In patients with COVID-19, dose adjustment of calcineurin and/or mTOR inhibitors might be required depending on the antiviral therapy initiated
RFA	• Select patients at low risk due to tumor location	• RFA should be postponed whenever possible

(*Continues*)

Table 1. (Continued)

	ILCA[7,8]	EASL[9]
	• Select patients with highest chance of cure; single tumors <3 cm • Assess risks and benefits in patients with comorbidities that increase the risk of serious infection from COVID-19 **Alternative/holding therapy: TA(C)E, SBRT, systemic therapy, active monitoring with imaging**	
TACE	• Select patients at lower risk of decompensation • Assess risks and benefits in patients with comorbidities that increase the risk of serious infection from COVID-19 • Consider use of prognostic scores such as HAP or beyond-seven criteria to select patients most likely to benefit • Consider use of TAE, DEB-TACE, or TARE to reduce risk of immunosuppression **Alternative therapy: systemic therapy, active monitoring with imaging**	• TACE should be postponed whenever possible
Systemic therapy	• For patients in clinical trials, discussion with sponsors required to accommodate variations in follow-up schedule, trial-related procedures and treatment location • Select patients most likely to benefit, based on performance status, Child–Pugh score and comorbidities • First-line sorafenib or lenvatinib to replace trial recruitment and minimize hospital visits • In regions where checkpoint inhibitors are approved, consider increased risks associated with attendance for infusion • Manage patients by telemedicine to avoid hospital visits Dispense drugs by mail, perform blood and urine tests, and measure BP locally in the community; consider omitting radiology response assessment and continue evaluating clinical progression by tolerance **Alternative therapy: active monitoring (with imaging where appropriate), supportive palliative care**	•Temporarily withdraw immune checkpoint inhibitor therapy Decide whether to continue/reduce TKI in patients with non-severe COVID-19 on a case-by-case basis

AFP, alpha-fetoprotein; BP, blood pressure; DEB-TACE, drug-eluting beads transarterial chemoembolization; EASL, European Association for the Study of the Liver; HAP; HCC, hepatocellular carcinoma; ILCA, International Liver Cancer Association; MELD, model for end-stage liver disease; NA, not applicable; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor.

ensuing disastrous collapse of the healthcare system. However, it is important that physicians and surgeons who are involved in the management and treatment of patients with liver diseases prepare for the worst-case scenario.

COVID-19 INFECTION AND LIVER DYSFUNCTION

LIVER DYSFUNCTION, MAINLY revealed by abnormal serum concentrations of aspartate transaminase and alanine transaminase, and a slight increase in bilirubin concentration, has been seen in 15%–78% of patients infected with COVID-19.[17–24] Liver dysfunction in patients with mild COVID-19 seem transient and may resolve without treatment. Serum albumin concentrations are reduced in patients with severe COVID-19 infection. Although the mechanism underlying the development of hypoalbuminemia in these patients is unknown, it likely involves inflammation and undernutrition. Increased concentrations of γ-glutamyl transferase, a biomarker for cholangiocyte injury, have been observed in 54% of patients infected with COVID-19.[19]

Table 2 Reports of COVID-19 infection in patients with cancer

Rate of COVID-19 infection	Rate of COVID-19 infection in cancer patients				
Yu et al.[14]	Yu et al.[14]	Liang et al.[15]	Zhang et al.[16]	Wang et al.[17]	Desai et al.[13]
• 41152 (0.37%) of 11081000 patients were COVID-19 infected*	• 12 (0.79%) of 1524 patients with COVID-19 had cancer Breakdown: Lung cancer, 7 Rectal cancer, 1 Colon cancer, 1 Pancreatic cancer, 1 Breast cancer, 1 Urothelial cancer, 1	• 18 (1.13%) of 1590 patients with COVID-19 had a history of cancer Breakdown: Lung cancer, 5 Colon cancer, 4 Breast cancer, 2 Bladder cancer, 2	• 28 (2.19%) of 1276 patients with COVID-19 had cancer Breakdown: Lung cancer, 7 Esophageal cancer, 4 Breast cancer, 3 Laryngeal cancer, 2 HCC, 2 Prostate cancer, 2	• 10 (7.24%) of 138 patients with COVID-19 had cancer Breakdown unknown	Meta-analysis of 11 studies, including 3661 patients, found that the rate of COVID-19 infection in patients with cancer was 2.0% (95% CI, 2.0–3.0). Sample size ≤100 3.0% (95% CI, 1.0–6.0) Sample size 100 2.0% (95% CI, 1.0–3.0)

*Number and percentage of patients with COVID-19 reported in Wuhan City.
CI, confidence interval; HCC, hepatocellular carcinoma.

A comparison of patients with severe and mild COVID-19 infection showed a significant deterioration of liver function in the former.[25,26] Similar to SARS-CoV, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) as a receptor to facilitate its entry into target cells. ACE2 is expressed on hepatocytes and cholangiocytes, with much higher expression levels in cholangiocytes (20-fold). Thus, the mechanism underlying the development of liver dysfunction in COVID-19 may involve injury to cholangiocytes and hepatocytes,[18,27,28] as well as immune-mediated liver injury and hypoxemia.[18,27] Post-mortem biopsy showed macrovesicular steatosis of the liver alongside mild lobular and portal inflammatory activity, suggesting either SARS-CoV-2 infection or drug-induced injury as the cause of liver dysfunction.[29]

Taken together, these findings suggest that liver function should be assessed in patients with COVID-19 by measuring concentrations of alanine transaminase, aspartate transaminase, alkaline phosphatase, γ-glutamyl transferase, albumin, total protein and total bilirubin, as well as prothrombin time or INR. Liver function should also be monitored regularly in all infected patients, particularly those with severe COVID-19, and those treated with investigational or off-label drugs.

HEPATOCELLULAR CARCINOMA TREATMENT WITH MEASURES TO REDUCE THE RISK OF COVID-19

THIS GUIDANCE WAS developed based on the likelihood that delivering standard HCC treatment[11,30] would come under strain in some institutions due to the COVID-19 pandemic. The situation is likely to vary depending on institution and timing, emphasizing the importance of careful balancing between the benefits of HCC treatment and the risks of COVID-19 infection in individual patients.

Table 3 Treatment of HCC considering reduction of COVID-19 infection risk

	Working Group for Japan Association of Molecular Targeted Therapy for HCC
General matters	• Where feasible, cancer therapy should be offered in a "COVID-free" institution, defined as an institution with no patients with COVID-19, or in an institution specializing in HCC treatment with a small number of COVID-19 cases who are completely under control to avoid nosocomial infection • Care should be maintained according to guidelines, to prevent hospital-acquired COVID-19 infection while securing sufficient beds for patients with COVID-19 • Alternative therapies and ways to avoid hospitalization and reduce hospital visits as much as possible should be considered after consultation with individual patients • Although use of telemedicine is desirable, treatment according to the regional environment, such as extending the interval between hospital visits and telephone follow-up for monitoring, is recommended
Surgical resection	• Screening by polymerase chain reaction testing before surgery to prevent transmission of COVID-19 to healthcare professionals • Select patients without comorbidities that increase the risk of severe COVID-19 • Postpone surgery whenever possible, based on macroscopic tumor classification, differentiation, and grade of malignancy with tumor marker • Consider alternative treatments such as RFA and bridging systemic therapy to shorten the in-hospital stay or to avoid hospitalization[32] **Alternative therapies: RFA, bridging systemic therapy**
RFA	• Postpone RFA whenever possible, based on macroscopic tumor classification, differentiation and grade of malignancy • Assess risks and benefits in patients with comorbidities that increase the risk of serious infection from COVID-19 • Consider alternative treatments such as bridging systemic therapy to avoid in-hospital stay **Alternative therapy: systemic therapy**
TACE	• Postpone TACE whenever possible, based on macroscopic tumor classification, differentiation and grade of malignancy • Assess risks and benefits in patients with comorbidities that increase the risk of serious infection from COVID-19 • Use prognostic factors such as up-to-seven criteria and ALBI grade to select appropriate patients for TACE (up-to-seven in) and systemic therapy (up-to-seven criteria out, mALBI grade 2b)[7,31,33-35] • Consider alternative treatment, such as systemic therapy (preferably lenvatinib) for TACE-unsuitable patients (simple nodular type with extranodular growth type, confluent multinodular type, poorly differentiated type, etc.), based on macroscopic tumor classification and differentiation[31,35-38] **Alternative therapy: systemic therapy (lenvatinib, etc.)**
Systemic therapy	• Select patients most likely to benefit based on PS, ALBI grade, Child–Pugh score and comorbidities • If risk of COVID-19 infection is high at the time of approval of immune checkpoint inhibitors, consider temporarily withdrawing or delaying immune checkpoint inhibitors to reduce frequency of hospital visits and infection risk in accordance with ILCA and EASL guidance[7-9,39-42] • Select oral medications or infusion regimens to reduce the frequency of hospital visits and to manage side effects • If patients are well-managed, consider reducing the frequency of hospital visits and follow-up by telephone
HAIC	• Prioritize systemic therapy instead of HAIC, avoiding in-hospital stay • Avoid regimens that cause neutropenia and thrombocytopenia and that require long hospitalization as much as possible • Assess risks and benefits in patients with comorbidities that increase the risk of serious infection from COVID-19 • Select patients likely to benefit, including those refractory to systemic therapy with advanced vascular invasion[31,43-45] **Alternative therapy: systemic therapy**

ALBI, albumin–bilirubin; EASL, European Association for the Study of the Liver; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ILCA, International Liver Cancer Association; PS, performance status; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

General matters

Patients with cancer are at high risk of COVID-19 infection because they are prone to infections in general, due to systemic immunosuppression resulting from anticancer treatment (e.g., chemotherapy).[13] Moreover, patients with cancer infected with COVID-19 are likely to have a

poor prognosis.[14,15] Accordingly, similar to the recommendations of the ILCA guidelines,[7] patients with HCC should be treated at COVID-19-free institutions, when feasible. COVID-19-free institutions are defined as medical institutions with no patients with COVID-19 or those specializing in HCC treatment with a small number of patients with COVID-19 who are completely under control to avoid nosocomial infection. Patients should be managed according to the Guidelines for Management of Liver Cancer,[11] but some modifications in HCC treatment strategies may be necessary if hospital admission and hospital stay for patients without COVID-19 are restricted to prevent nosocomial infection, and to secure beds for patients with COVID-19.[7,8]

Use of telemedicine is desirable but has not yet been established in Japan. Thus, measures should reflect regional circumstances, such as extending the interval between hospital visits and conducting follow-up examinations by telephone.[7,8]

Hospitalization is required for many procedures in HCC treatment, such as surgical resection, RFA, TACE and hepatic arterial infusion chemotherapy (HAIC). In Japan, surgical resection and RFA are the main treatment options for patients with Barcelona Clinic Liver Cancer (BCLC) stage A HCC; TACE and molecular targeted therapy are options for patients with BCLC stage B HCC; and molecular targeted therapy and HAIC are options for BCLC stage C HCC.[11,30,31] Treatment in compliance with the guidelines is fundamental and important, even during the COVID-19 pandemic; however, treatment that reduces the risk of COVID-19 must also be considered. To avoid nosocomial COVID-19 and to ensure adequate inpatient beds for patients with COVID-19, hospital admission for HCC treatment should be avoided when feasible, and alternative or modified treatment modalities that can reduce the frequency of visits to healthcare facilities should be considered after fully discussing available options with the patient (Table 3). Further spread of COVID-19 will warrant examining the benefits of performing or postponing treatment for HCC from several perspectives, including the medical perspective and the perspective of efficient and effective allocation of medical resources. Shortages of healthcare staff, inpatient beds and resources (e.g., personal protective equipment) in some institutions, as has happened in Europe and in some institutions in Japan, would preclude the treatment of HCC at those institutions. When feasible, these patients should therefore be referred to COVID-19-free institutions.

Surgical resection and liver transplantation

To avoid transmission of COVID-19 to healthcare professionals, patients should be tested for COVID-19 using the polymerase chain reaction assay before surgery. Patients without comorbidities who are at increased risk of severe COVID-19 infection must be selected. Patients not requiring emergency surgery, based on the macroscopic classification, degree of differentiation and staging of the tumor, should be advised to avoid hospital admission by postponing surgery. The results of the surgery versus RFA (SURF) trial indicate that RFA, the less invasive option, should be proactively considered if there are ≤3 nodules each measuring ≤3 cm, which would shorten hospital stay.[32] If postponing surgical resection is considered, tumor growth should be suppressed using alternative outpatient therapy, such as bridging systemic therapy, with surgery rescheduled after carefully evaluating the risks and benefits of hospital admission in light of the COVID-19 pandemic.

Regarding the surgical resection and liver transplantation, other guidance by American College of Surgeons and Japan Society for Transplantation may also be useful to follow.[46,47]

Radiofrequency ablation

Before RFA, macroscopic classification, tumor differentiation and tumor stage (size and number of nodules) should be evaluated. If the risks of RFA, including the risk of complications, exceed its benefits, RFA should be postponed when feasible. Alternatively, patients should be referred or transferred to a COVID-19-free institution. Even when the benefits of RFA exceeds its risks, particularly if an institution is on the verge of collapse, with obvious shortages of staff and resources, such as personal protective equipment and inpatient beds, hospital admission should be postponed and patients should be treated with alternative tumor growth suppression therapy, such as bridging systemic therapy, or transferred to a COVID-19-free institution for RFA.

Transarterial chemoembolization

TACE should be considered based on the macroscopic classification, degree of differentiation and tumor stage. The risk of complications and the risks and benefits of TACE should be assessed for patients with comorbidities that carry increased risks of severe COVID-19. The need for TACE should be evaluated by assessing indices such as the up-to-seven criteria[48] and albumin–bilirubin (ALBI) grade.[49] Systemic therapy should be considered for

patients not indicated for TACE, including those classified as up-to-seven criteria OUT patients or patients with ALBI grade 2 (particularly mALBI grade 2b).[33-35,50-54] Systemic therapy should also be considered when TACE is not indicated based on macroscopic classification and degree of differentiation, which include tumors beyond simple nodular type with extranodular growth, confluent multinodular type or poorly differentiated type.[35-37,55] Avoiding or postponing hospital admission and replacing TACE with systemic therapy, preferably using agents with high response rates such as lenvatinib, should be considered.[39,56,57]

Systemic therapy

The patients most likely to benefit from systemic therapy should be selected based on performance status, ALBI grade, Child–Pugh score and comorbidities. Immune checkpoint inhibitors have not yet been approved for HCC treatment in Japan (as of July 2020). If the risk of COVID-19 remains high when immune checkpoint inhibitors are approved, the interval between hospital visits should be extended to reduce the frequency of visits and the risk of COVID-19, as recommended by the ILCA and EASL and other guidelines.[7,39–42] The selection of oral administration agents such as tyrosine kinase inhibitors or injection agents such as ramucirumab should be considered carefully to reduce the frequency of visits and consequent risks of infection by considering the required management of likely adverse events. Patients are recommended to stay home more strictly than patients without cancer as patients who are receiving systemic therapy are at higher risk of a fatal condition due to COVID-19.[15] Once systemic therapy has started, use of telephone-based consultations should be considered, enabling careful monitoring of patients without the need for frequent hospital visits over a short period. Reducing the frequency of hospital visits and telephone-based consultations should be considered in individual patients in a stable condition who have been on systemic therapy for a while without problems (e.g., adverse reactions).

Hepatic arterial infusion chemotherapy

The decision to perform HAIC should be based on assessment of both its necessity and risks, as well as the risk of COVID-19 infection associated with catheter placement in the hepatic artery. In the absence of obvious vascular invasion, systemic therapy is the preferred option.[43–45,58] In addition, HAIC with regimens of cytotoxic anticancer agents that cause neutropenia and thrombocytopenia, or that require long hospital stays and frequent hospital visits, should be avoided as much as possible. Similarly, the risks and benefits of HAIC should be evaluated in patients with comorbidities that increase the risk of severe COVID-19. HAIC should be considered if it can benefit such patients, including those unresponsive to systemic therapy or advanced vascular invasion.[11,31,43–45] However, when institutions face strains because of COVID-19, patients should be referred to COVID-19 free institutions.

Clinical trials

Regulatory authorities have already published guidance on how to handle the clinical trials during the COVID-19 pandemic with the main principle on the flexibility of implementing trial procedures to protect patients.[59–61]

The safety of trial participants should always be the top priority in decision making and conducting clinical trials. Therefore, the benefit/risk assessment should be always monitored during conduct of clinical trials during the COVID-19 outbreak. When a trial subject is at excessive risks due to trial procedures or treatments, modification or even interruption of accrual should be considered. Owing to the COVID-19 outbreak, the number of protocol deviations is expected to increase during the COVID-19 pandemic. Therefore, it is important for investigators to document the protocol deviation and closely communicate with the regulatory authorities and sponsor companies. When the supply of study medications is interrupted, patients should be considered alternative systemic therapy for HCC, such as sorafenib or lenvatinib as ILCA guidance suggests.[7]

CLOSING REMARKS

THIS CONTINGENCY GUIDE was developed for two main reasons. First, the spread of COVID-19 in metropolitan areas in the Tokyo and Osaka regions, as well as in Hokkaido and Fukuoka, led to shortages of inpatient beds, healthcare staff and other resources (e.g., personal protective equipment), particularly at institutions that received patients with moderate to severe COVID-19. Thus, these affected institutions could not provide patients with standard HCC therapy. Second, it is vital to prepare for the same situation that may occur during the second and third waves of the COVID-19 pandemic. Although many institutions will likely be able to provide standard therapy for HCC as of July, 2020, when current restrictions are lifted, the second and third waves are projected to occur within a year, making it extremely important to determine how to deliver HCC treatments when institutions will likely come close to collapse. The authors hope that Japan can avoid an explosive surge of infections and the consequent disastrous effects on the healthcare system, as already seen

in Europe and the United States. Therefore, this contingency guide was developed to ensure continued delivery of HCC treatment should the system become overwhelmed.

We hope this guide may help institutions design programs to guarantee continued delivery of HCC treatment under the strain of the COVID-19 pandemic.

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