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 Torimura6 and Naoya Sakamoto7

1Department of Gastroenterology and Hepatology, Faculty of Medicine, Kindai University, 2Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, 3Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, 4Department of Gastroenterology and Metabolism, Graduate School of Biomedical and Health Science, Hiroshima University, 5Department of Gastroenterology, Ehime Prefectural Central Hospital, 6Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, and 7Department 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, including 20,174 infected patients, with 980 deaths, in Japan. 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. 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.
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), European Society for Medical Oncology (ESMO), National Institute for Health and Care Excellence (NICE) and the Japanese Society of Medical Oncology (JSMO). Similarly, clinical practice guidance for liver diseases and liver cancer has been released to healthcare professionals by the International Liver Cancer Association (ILCA), the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) (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. 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.

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), 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.

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, and COVID-19 infection has been found to increase mortality rates in patients with cancer. (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. 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.

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). 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. 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). 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%). 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. 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<sup>7,8</sup> | EASL<sup>9</sup> |
|-------------------|------------------|
| **General matters** |                  |
| • Reduce hospital visits and use telemedicine to prevent hospital-acquired COVID-19 infection | • 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 |
| • Where visits cannot be avoided, use personal protective equipment in line with national guidance | • Early admission is recommended for patients with COVID-19 |
| • 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 | |
| **Surgical resection** | NA |
| • Select patients with lower risk of decompensation | |
| • Select patients without comorbidities that increase the risk of severe COVID-19 | |
| **Transplant** | |
| • Temporary suspension of elective living donor transplantation may be considered to protect both the potential donor and recipient | • 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 |
| • 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 | • 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 |
| **Alternative/holding therapy:** ablation if anesthetic capacity allows, Bridging TA(C)E, SBRT, bridging systemic therapy, active monitoring with imaging | |
| **RFA** | |
| • Select patients at low risk due to tumor location | • In patients with COVID-19, dose adjustment of calcineurin and/or mTOR inhibitors might be required depending on the antiviral therapy initiated |
| | • RFA should be postponed whenever possible |

(Continues)
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 \(\gamma\)-glutamyl transferase, a biomarker for cholangiocyte injury, have been observed in 54% of patients infected with COVID-19.\(^{19}\)

\[\text{© 2020 The Authors.} \]

Hepatology Research published by John Wiley & Sons Australia, Ltd on behalf of Japan Society of Hepatology
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 treatment11,30 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 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               | • 41152 (0.37%) of 11081000 patients were COVID-19 infected* |
| Liang et al.15            | • 12 (0.79%) of 1524 patients with COVID-19 had cancer |
| Zhang et al.16            | • 18 (1.13%) of 1590 patients with COVID-19 had a history of cancer |
| Wang et al.17             | • 28 (2.19%) of 1276 patients with COVID-19 had cancer |
| Desai et al.13            | • 10 (7.24%) of 138 patients with COVID-19 had cancer |

| Rate of COVID-19 infection in cancer patients |
|---------------------------------------------|
| 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). |

Breakdown: Lung cancer, 7

Rectal cancer, 1
Colorectal cancer, 1
Pancreatic cancer, 1
Breast cancer, 1
Urothelial cancer, 1

Breakdown:
Lung cancer, 7
Esophageal cancer, 4
Breast cancer, 3
Laryngeal cancer, 2
HCC, 2
Prostate cancer, 2

Breakdown:
Lung cancer, 5
Colon cancer, 4
Breast cancer, 2
Bladder cancer, 2

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

© 2020 The Authors.
Hepatology Research published by John Wiley & Sons Australia, Ltd on behalf of Japan Society of Hepatology
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). Moreover, patients with cancer infected with COVID-19 are likely to have a

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 |
| 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  |
| 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)  
  • 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 |
| 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  
  • 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  |

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.

© 2020 The Authors. Hepatology Research published by John Wiley & Sons Australia, Ltd on behalf of Japan Society of Hepatology
poor prognosis.\textsuperscript{14,15} Accordingly, similar to the recommendations of the ILCA guidelines,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 exceed 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\textsuperscript{48} and albumin–bilirubin (ALBI) grade.\textsuperscript{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.59,56,57

**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.

REFERENCES
1 World Health Organization (WHO): Coronavirus disease (COVID-19) Pandemic 2020; Available from: https://covid19.who.int/
2 The Ministry of Health, Labour and Welfare. Latest information on coronavirus disease 2019 (COVID-19). Available from: https://www.mhlw.go.jp/stf/seisakuunitsuite/bunya/topics_shingata_09444.html
3 American Society of Clinical Oncology (ASCO): Coronavirus Resources; Available from: https://www.asco.org/asco-coronavirus-information
4 European Society for Medical Oncology (ESMO): COVID-19 and cancer; Available from: https://www.esmo.org/covid-19-and-cancer
5 COVID-19 rapid guideline: delivery of systemic anticancer treatments. https://wwwniccorguk/guidance/ng161.
6 Japanese Society of Medical Oncology (JSMO): Information on novel coronavirus disease; Available from: https://www.jsmo.or.jp/ (in Japanese).
7 International Liver Cancer (ILCA): COVID-19 & Liver Cancer. Available from: https://ilca-online.org/covid19andlivercancer/
8 International Liver Cancer (ILCA): MANAGEMENT OF HCC DURING COVID-19 ILCA GUIDANCE; Available from: https://mcusercontent.com/ab4445175c75a57073d4ad02d/files/04c3c6de-7f63-4bb6-86a3-6c3e56242728/ILCA_COVID_19_.pdf
9 Boettler T, Newsome PN, Mondelli MU et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Rep Innov Hepatol 2020; 2: 100113.
10 AASLD Clinical Insights for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic. https://easleu-news/easl-escmid-position-paper-on-covid19-and-the-liver/.
11 Kokudo N, Takemura N, Hasegawa K et al. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepato Res Off J Japan Soc Hepatol 2019; 49: 1109–13.
12 Kudo M, Kurosaki M, Ikeda M, et al. Guidance for treatment of hepatocellular carcinoma (HCC) during the COVID-19 outbreak: The Working Group Report of JAMIT-HCC. Kanzo, 2020 (in Japanese) [in submission].
13 Desai A, Sachdeva S, Parekh T, Desai R. COVID-19 and Cancer: Lessons From a Pooled Meta-Analysis. JCO Global Oncol 2020; 6: 557–9.
14 Yul, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. JAMA Oncol 2020; 6(7): 1108. https://doi.org/10.1001/jamaoncol.2020.0980
15 Liang W, Guan W, Chen R et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21: 335–7.
16 Zhang L, Zhu F, Xie L et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol Off J Eur Soc Med Oncol 2020; 31: 894–901.
17 Wang D, Hu B, Hu C et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061–9.
18 Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int Off J Int Assoc Stud Liver 2020; 40: 998–1004.
19 Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020; 5: 428–30.
20 Chen N, Zhou M, Dong X et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England) 2020; 395: 507–13.
21 Shi H, Han X, Jiang N et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020; 20: 425–34.
22 Zhao D, Yao F, Wang L et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. Clin Infect Dis Off Publ Infect Dis Soc Am 2020; https://doi.org/10.1093/cid/ciaa247
23 Yang X, Yu Y, Xu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475–81.
24 Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020; 395: 497–506.
25 Guan WJ, Ni ZY, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708–20.
26 Cai Q, Huang D, Ou P et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020. https://doi.org/10.1111/all.14309
27 Chai X, Hu L, Zhang Y et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. bioRxiv 2020; 2020.2002.2003.931766.
28 Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. J Gastroenterol Hepatol 2020; 35: 744–8.
29 Xu Z, Shi L, Wang Y et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8: 420–2.
30 Ikeda K. Recent advances in medical management of hepatocellular carcinoma. Hepatol Res Off J Japn Soc Hepatol 2019; 49: 14–32.

© 2020 The Authors.
Hepatology Research published by John Wiley & Sons Australia, Ltd on behalf of Japan Society of Hepatology
The Japan Society of Hepatology: Clinical practice manual for hepatocellular carcinoma, ver. 4, Igakushoin, Tokyo, 2020 (in Japanese).

Izumi N, Hasegawa K, Nishioka Y et al. A multicenter randomized controlled trial to evaluate the efficacy of surgery vs radiofrequency ablation for small hepatocellular carcinoma (SURF trial). J Clin Oncol 37, 4002(suppl 15): 2019 [ASCO 2019, LBA].

Kudo M. A New Treatment Option for Intermediate-Stage Hepatocellular Carcinoma with High Tumor Burden: Initial Lenvatinib Therapy with Subsequent Selective TACE. Liver Cancer 2019; 8: 299–311.

Kudo M, Ueshima K, Chan S et al. Lenvatinib as an Initial Treatment in Patients with Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven Criteria and Child-Pugh A Liver Function: A Proof-Of-Concept Study. Cancer 2019; 11: 92.

Kawamura Y, Kobayashi M, Shindo I et al. A Pretreatment heterogeneous enhancement pattern of hepatocellular carcinoma may be a useful new predictor of early response to lenvatinib and overall prognosis. Liver Cancer 2020; 9: 275–92.

Kudo M, Finn RS, Qin S et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet (London, England) 2018; 391: 1163–73.

Gillessen S, Powles T. Advice Regarding Systemic Therapy in Patients with Urological Cancers During the COVID-19 Pandemic. Eur Urol 2020; 77: 667–8.

EAU Guidelines Office Rapid Reaction Group: An organisation-wide collaborative effort to adapt the EAU guidelines recommendations to the COVID-19 era; Available from: https://uroweb.org/guideline/covid-19-recommendations

NCCN Short-Term Recommendations for Non-Small Cell Lung Cancer Management During the COVID-19 Pandemic; Available from: https://www.nccn.org/covid-19/pdf/COVID_NSCLC.pdf

ESMO management and treatment adapted recommendations in the COVID-19 era: Breast cancer; Available from: https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/breast-cancer-in-the-covid-19-era

Kudo M, Ueshima K, Yokosuka O et al. Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. Lancet Gastroenterol Hepatol 2018; 3: 424–32.

Ogasawara S, Ueshima K, Ikeda M et al. Sorafenib versus hepatic arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma: A Japanese multi-center large cohort study. J Clin Oncol 2019(suppl: abstr 323); 37: 323.

He M, Li Q, Zou R et al. Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin vs Sorafenib Alone for Hepatocellular Carcinoma With Portal Vein Invasion: A Randomized Clinical Trial. JAMA Oncol 2019; 5: 953–60.

American College of Surgeons: COVID-19 and Surgery; https://www.facs.org/covid-19/clinical-guidance

Japan Society for Transplantation: Guidance for transplantation during COVID-19 pandemic, ver. 4, May 29, 2020. https://square.umin.ac.jp/jst-covid-19/images/guidance4.pdf

Bolondi L, Burroughs A, Dufour JF et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012; 32: 348–59.

Johnson PL, Berhane S, Kageyashashi C et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol Off J Am Soc Clin Oncol 2015; 33: 550–8.

Kimura H, Ohkawa K, Miyazaki M et al. Subclassification of patients with intermediate-stage (Barcelona Clinic Liver Cancer stage B) hepatocellular carcinoma using the up-to-seven criteria and serum tumor markers. Hepat Int 2017; 11: 105–14.

Eso Y, Takai A, Takahashi K et al. Combination of Mac-2 Binding Protein Glycosylation Isomer and Up-To-Seven Criteria as a Useful Predictor for Child-Pugh Grade Deterioration after Transarterial Chemoembolization for Hepatocellular Carcinoma. Cancer 2019; 11.

Hiraoa A, Kumada T, Tsuji K et al. Validation of Modified ALBI Grade for More Detailed Assessment of Hepatic Function in Hepatocellular Carcinoma Patients: A Multicenter Analysis. Liver Cancer 2019; 8: 121–9.

Izumoto H, Hiraoa K, Ishimaru Y et al. Validation of Newly Proposed Time to Transarterial Chemoembolization Progression in Intermediate-Stage Hepatocellular Carcinoma Cases. Oncology 2017; 93(Suppl 1): 120–6.

Ueshima K, Nishida N, Hagiwara S et al. Impact of Baseline ALBI Grade on the Outcomes of Hepatocellular Carcinoma Patients Treated with Lenvatinib: A Multicenter Study. Cancer 2019; 11.

Kawamura Y, Ikeda K, Hirakawa M et al. New classification of dynamic computed tomography images predictive of malignant characteristics of hepatocellular carcinoma. Hepatol Res Off J Japn Soc Hepatol 2010; 40: 1006–14.

Yamashita T, Kudo M, Ikeda K et al. REFLECT-a phase 3 trial comparing efficacy and safety of lenvatinib vs sorafenib for the treatment of unresectable hepatocellular carcinoma: an analysis of Japanese subset. J Gastroenterol 2020; 55: 113–22.
57 Kudo M. Extremely High Objective Response Rate of Lenvatinib: Its Clinical Relevance and Changing the Treatment Paradigm in Hepatocellular Carcinoma. Liver Cancer 2018; 7: 215–24.
58 Ikeda M, Shimizu S, Sato T et al. Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial. Ann Oncol Off J Eur Soc Med Oncol 2016; 27: 2090–6.
59 European Medicines Agency: Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic. https://www.ema.europa.eu/en/documents/press-release/
guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic_en.pdf
60 U.S. Food & Drugs Administration: FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. https://www.fda.gov/media/136238/download
61 Medicines and Healthcare Products Regulatory Agency: Managing clinical trials during Coronavirus (COVID-19). https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19