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Surgical treatment of hepatocellular carcinoma in the era of COVID-19 pandemic: A comprehensive review of current recommendations

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Abstract

The new coronavirus disease 2019 (COVID-19) pandemic has resulted in a global health emergency that has also caused profound changes in the treatment of cancer. The management of hepatocellular carcinoma (HCC) across the world has been modified according to the scarcity of care resources that have been diverted mostly to face the surge of hospitalized COVID-19 patients. Oncological and hepatobiliary societies have drafted recommendations regarding the adaptation of guidelines for the management of HCC to the current healthcare situation. This review focuses on specific recommendations for the surgical treatment of HCC (*i.e.*, hepatic resection and liver transplantation), which still represents the best chance of cure for patients with very early and early HCC. While surgery should be pursued for very selected patients in institutions where standards of care are maintained, alternative or bridging methods, mostly thermoablation and transarterial therapies, can be used until surgery can be performed. The prognosis of patients with HCC largely depends on both the characteristics of the tumour and the stage of underlying liver disease. Risk stratification plays a pivotal role in determining the most appropriate treatment for each case and needs to balance the chance of cure and the risk of COVID-19 infection during hospitalization.

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Current recommendations have been critically reviewed to provide a reference for best practices in the clinical setting, with adaptation based on pandemic trends and categorization according to COVID-19 prevalence.

Key Words: Hepatocellular carcinoma; COVID-19; Hepatic resection; Liver transplant; Ablation

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Core Tip: Guidelines on the surgical management of hepatocellular carcinoma have been recently adapted to the prioritization of health resources to the care of patients with coronavirus disease 2019 (COVID-19). There has been a reduction in hepatic resection and liver transplant activity, which need to be restricted to very selected cases. For patients in whom surgery cannot be performed in due time, alternative or delaying strategies, mostly ablation or transarterial therapies, should be considered. The decision on surgical management should be based on risk stratification and the balance between the increased risk of COVID-19 infection, the urgency of the intervention, and the oncological effects of delayed treatment and shared with patients.

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INTRODUCTION

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for coronavirus disease 2019 (COVID-19), which has been spreading worldwide since the end of 2019, causing a global health system crisis[1-3]. Along with serious effects on the patients affected by the new coronavirus infection, the pandemic has also led to deleterious repercussions on patients affected by other diseases. In fact, the global health organization has been reshaped to face the rapid spread of the COVID-19 pandemic. On all continents, hospital systems are addressing the increasing volume of admissions of patients with the new coronavirus disease, thus delaying elective surgery and diagnostic procedures[4-6]. As a consequence, the COVID-19 outbreak has had profound effects on the management of cancer patients. In this regard, hepatocellular carcinoma (HCC) is globally recognized as a leading cause of cancer-related death, with more than 780000 deaths registered in 2018[1,7-9]. Although advances have been made in prevention, early diagnosis, and multimodality treatment over the past few decades, the incidence and cancer-specific mortality of HCC continue to remain high in many countries, mostly in Southeast Asia and Africa, where the incidence is predominant[10,11]. The management of HCC represents a major issue in the current scenario, also because it is uncertain how long the limitations in health service delivery will last. Useful recommendations from oncological and hepatobiliary societies have aimed to offer guidance on how to approach the burden of patients requiring treatment for HCC. This review aims to critically evaluate the impact of the COVID-19 outbreak on the clinical care and surgical management of patients with HCC. We also provide evidence-based guidance for the management of patients with HCC amenable to surgical treatment based on recommendations from the most highly regarded scientific societies, as well as from experience with large case series from high-volume hepatobiliary centres.

LITERATURE SEARCH AND REVIEW DESIGN

The present review focused on the surgical treatment of HCC, including hepatic resections and liver transplantation. A systematic literature search using the PubMed, Web of Science, and Scopus databases was performed in December 2020 to identify

studies reporting on the management of HCC during the COVID-19 pandemic. The following keywords were used and combined for the search: “hepatocellular carcinoma”, “HCC”, “liver cancer”, “surgical treatment”, “hepatectomy”, “hepatic resection”, “liver transplant”, “SARS-CoV-2”, and “COVID-19”. Reference lists were searched manually to identify further studies. In addition, guidelines of the principal oncological, hepatobiliary, transplant societies and organizations, position papers, cohort studies, and expert opinions were manually searched on the web. A resume of recommendations released from scientific societies and institutions on the surgical treatment of HCC during the COVID-19 pandemic was reported in [Table 1](#).

CURRENT SCENARIO OF HCC TREATMENT

As with other tumours, the treatment of HCC has been impaired since the beginning of the new coronavirus disease. A review of the literature revealed different algorithms for the management of HCC, mostly because the aetiology and epidemiology of HCC vary across countries worldwide[12]. Nonetheless, surgical treatment (*i.e.*, hepatic resection or liver transplantation) is the most likely chance of cure for selected patients with HCC[8,9,13]. In the present scenario of the global pandemic, the surgical management of HCC undoubtedly presents more objective difficulties than other fields of surgical oncology. In fact, in many cases, surgical interventions for HCC, increase the risk for intensive care unit need, blood transfusion requirement, and prolonged hospitalization[9,10,14]. In particular, major hepatectomy and blood transfusions are independent risk factors for an intensive care unit stay after surgery[15]. The need for an intraoperative or postoperative blood transfusion represents an important issue due to possible blood shortages related to the COVID-19 pandemic[16,17].

The Italian Association for the Study of the Liver conducted a survey to evaluate the impact of COVID-19 on the activity of some hepatology units, reporting that the surgical treatment of HCC had been significantly reduced or even stopped. In particular, surgical and nonsurgical locoregional procedures for the management of HCC were reduced (44% and 34%, respectively) or suspended (44% and 8%, respectively) in the centres involved in the study[18].

In a recent study from six academic referral centres in France, the authors reported a delay longer than one month in the treatment of HCC in 2020 compared to 2019 (pre-COVID era), and the COVID period was found to be a strong independent predictor of treatment delay or cancellation[4]. In another recent survey, only 10% of respondents reported that cancer surgery proceeded unaffected in the pandemic, with intensive care unit (ICU) bed availability being a major concern[1,9,13,14] ([Table 2](#)).

The reduced level of care in the management of HCC could be explained by decreased access to the operating room, interventional radiology facilities, postoperative intensive care units and ventilators, all of which are factors that force physicians to delay a patient’s treatment. However, the reasons behind the cancellation or postponement of HCC surgery during the pandemic are related not only to resource impairment but also to concerns about the consistent risk of developing COVID-19 infection during the hospital stay[13].

The American College of Surgeons (ACS) developed an Elective Surgery Acuity Scale to assist in the decision-making process not only for surgery but also for other actions concerning triage non-emergent interventions. HCC, as well as most other cancers, is categorized as “Tier 3a (high acuity)”; thus, action should not be postponed in general[19].

The surveillance of HCC in the high-risk population has also been impaired due to the COVID-19 outbreak, with many subjects undergoing liver ultrasound beyond the 6-mo surveillance interval usually considered a standard for high-risk subjects[10]. The authors observed a decreased number of cases of HCC in 2020 with respect to 2019 due to delays in diagnostic work-up[4]. This implies that more advanced HCC cases are expected in the near future.

EFFECTS OF SARS-COV-2 ON LIVER DISEASES AND HCC

Several studies underscored that patients with cancer affected from COVID-19 may be at higher risk of progression to severe disease, admission to intensive care unit, and death compared with patients without cancer[1,10,20-22]. On the other hand, COVID-19 infection increases mortality rates in patients with cancer[1,23-25]. The latter aspect

Table 1 Resume of scientific societies and institutions releasing recommendations addressing the surgical treatment of hepatocellular carcinoma during the coronavirus disease 2019 pandemic

Society/Institution	Date of release	Items addressed
AASLD (American Association for the Study of Liver Diseases)[20]	November 2020	Clinical best practice advice for hepatology and liver transplant providers during the COVID-19
APASL (Asian Pacific Association for the Study of the Liver)[46]	May 2020	Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic
APASL (Asian Pacific Association for the Study of the Liver)[10]	November 2020	Practical recommendations for the management of hepatocellular carcinoma in the era of COVID-19
E-AHPBA (European-African Hepato Pancreato-Biliary Association)[13]	June 2020	Delivery of hepato-pancreato-biliary surgery during the COVID-19 pandemic
EASL (European Association for the Study of the Liver)[48]	April 2020	Care of patients with liver disease during the COVID-19 pandemic
ESMO (European Society of Medical Oncology)[40]	April 2020	Management and treatment adapted recommendations in the COVID-19 era: hepatocellular carcinoma
ILCA (International Liver Cancer Association)[35]	April 2020	Management of HCC during COVID-19 pandemic
JAMMT (Working Group for Japan Association of Molecular Targeted Therapy for HCC)[23]	September 2020	Treatment of hepatocellular carcinoma during the COVID-19 outbreak
SAGES-AHPBA (Society of American Gastrointestinal and Endoscopic Surgeons- Americas Hepato-Pancreato-Biliary Association)[41]	April 2020	Recommendations regarding surgical management of HPB cancer patients during the response to the COVID-19 crisis
Saudi Association for the Study of Liver Disease and Transplantation[27]	June 2020	Principles of care for patients with liver disease during the COVID-19 pandemic
SSO (Society of Surgical Oncology)[43]	April 2020	Resource for management options of GI and HPB cancers during COVID-19

COVID-19: Coronavirus disease 2019; HCC: Hepatocellular carcinoma; GI: Gastrointestinal; HPB: Hepato-pancreato-biliary.

Table 2 Studies reporting on the surgical treatment of hepatocellular carcinoma in the pre-coronavirus disease and coronavirus disease era

Ref.	Treatment of HCC
Aghemo <i>et al</i> [18]	Surgical and nonsurgical locoregional procedures for management of HCC had been reduced (44% and 34%, respectively) or suspended (44% and 8%, respectively) in the centers involved in the study
Amaddeo <i>et al</i> [4]	Delay was longer than one month in the treatment of HCC in 2020, compared to 2019 (pre-COVID era)
Balakrishnan <i>et al</i> [13]	Only 10% of respondents in a cross-sectional survey reported that cancer surgery for HPB proceeded unaffected in the pandemic
Iavarone <i>et al</i> [63]	In a 4-wk period in 2020 compared with a 4-wk period in 2019, a lower number of patients submitted to surgical resection and liver transplant was observed
Siniscalchi <i>et al</i> [64]	Transplantation activities were reduced from February June 30, 2020, compared with the corresponding period in 2019
Soin <i>et al</i> [65]	In the period March-June 2020 the authors performed less living-donor liver transplantation than 2019 (39 vs 23)

HCC: Hepatocellular carcinoma; COVID-19: Coronavirus disease 2019; HPB: Hepato-pancreato-biliary.

may be related to the immunosuppressive effects of some anticancer treatments, as well as to advanced age and a poor performance status of the majority of patients affected by cancer[10].

In the majority of patients with HCC, underlying chronic liver disease (*e.g.*, HBV/HCV chronic hepatitis infection, alcoholic liver disease, and non-alcoholic fatty liver disease) is present[26,27]. In patients with chronic liver disease (approximately 1.5 billion people), impaired immune function could increase the risk of symptomatic COVID-19 infection[22,27-30]. Data from two international reporting registries showed a high mortality rate of 39.8% among COVID-19 patients with chronic liver disease[30]. While the impact of nonalcoholic fatty liver disease on COVID-19 is not well known, associated risk factors such as obesity, diabetes mellitus, and hyper-

tion are associated with COVID-19 severity[31].

SARS-CoV-2 is internalized into target cells through angiotensin-converting enzyme 2, which is present in biliary and liver epithelial cells, making the liver a potential target organ for infection[20,22]. The hypothesized effects of SARS-CoV-2 infection on existing chronic liver disease include potential viral reactivation in patients with chronic viral hepatitis induced by immunosuppression. In addition, the potential hepatotoxicity produced by drugs used for the treatment of the novel coronavirus infection (such as remdesivir and tocilizumab) may lead to hepatic decompensation in patients with reduced hepatic reserve[10,22,32-34]. Notably, elevated serum liver biochemistry levels are observed in 14% to 83% of hospitalized patients with COVID-19[10,22,35,36].

HEPATIC RESECTION OF HCC

The prognosis of patients with HCC largely depends on both the characteristics of the tumour and the stage of underlying liver disease. In general, prediction models commonly used for risk stratification may also help in the decision-making process regarding HCC during the COVID-19 outbreak. It has been shown that patients at highest risk after hepatic resection are those with comorbidities, age ≥ 75 years, underlying cirrhosis, and those necessitating biliary reconstruction, resection of ≥ 4 liver segments, and blood transfusions[16,37]. In candidates for hepatic resection, the risks and benefits of surgical intervention vary based on the extension of the planned resection, hepatic reserve, and SARS-CoV-2 infection risk. Furthermore, consideration of the need for postoperative ICU care rises to prominence in the COVID-19 scenario. The opportunity to carry out hepatic resection for HCC needs to be assessed on an individual basis by a multidisciplinary team and fully discussed with the patient[10,35,38]. For those in whom upfront hepatic resection represents the best chance of cure, surgery could be considered in the centres where HCC surgery is continued with the usual standards even during the COVID-19 emergency, especially for smaller, unifocal disease amenable to limited resection[9]. However, when hepatic resection is planned during the pandemic, two main concepts should be respected: hepatic resection should be restricted to (1) patients with a low risk of liver decompensation; and (2) those without comorbidities that increase the risk of severe COVID-19[10,35]. Furthermore, some authors discourage the use of major hepatectomies during the pandemic[38].

Although hepatic resection remains the option of choice for selected patients with early HCC, given the limitations in the management of HCC related to the pandemic, it has become clear that alternatives to the current standard of care are to be taken with the aim of postponing definitive therapy. In this regard, different approaches can be adopted when surgery is not feasible in due time.

A delaying strategy is active monitoring with imaging in selected cases[35]. There is a general agreement to delay the non-urgent treatment of localized HCC by 8–12 wk if oncological outcomes are unlikely to be affected[14]. In a Western series of 242 HCC patients, albeit heterogeneous, the median HCC doubling time was 229 d, with indolent growth mostly observed in large tumours with serum alpha-fetoprotein (AFP) levels < 20 ng/mL and in patients with non-viral (as opposed to viral) cirrhosis[39]. According to recommendations from the Japan Association of Molecular Targeted Therapy for Hepatocellular Carcinoma (JAMTT-HCC), surgical resection should be postponed whenever possible based on the macroscopic tumour classification, differentiation, and grade of malignancy with tumour markers[23]. Small solitary HCCs (< 2 cm) with no vascular invasion (especially if associated with a normal AFP level) may be safely observed until surgery can be performed because their risk for disease progression is low[38].

For HCC surveillance and diagnosis, incidental liver lesions < 1 cm are at low risk of disease progression; thus, an immediate evaluation with further imaging work-up and/or liver biopsy may be delayed[27]. According to the American Association for the Study of Liver Diseases consensus statement, the slow median doubling time of HCC sustains a short delay in radiological surveillance in areas of high COVID-19 prevalence[20]. It is of paramount importance to discuss with the patient and evaluate the risks and benefits of delaying HCC surveillance and diagnostic tests[27].

In cases where the treatment of HCC cannot be delayed, alternative treatments could be used to safely postpone or even substitute surgery. HCCs up to 3 cm can be treated with ablation instead of surgical resection, while larger tumours can be bridged with transarterial liver-directed therapy, such as transarterial chemoembo-

lization (TACE) or transarterial radioembolization (TARE), before surgical treatment[14].

Close work-up with imaging and AFP dosage is warranted in patients where bridging therapy or active monitoring is offered in place of potentially curative interventions to promptly identify patients at risk of tumour progression[28,35].

The European Society of Medical Oncology recommends “high priority” surgery with curative intent for patients with large or multifocal but still curatively resectable HCC lesions and “medium priority” curative surgical resection for patients with small, single HCC lesions[40].

The Society of Surgical Oncology (SSO) and Society of American Gastrointestinal and Endoscopic Surgeons-Americas Hepato-Pancreato-Biliary Association (SAGES-AHPBA) drafted recommendations on the surgical treatment of hepatobiliary cancers on the basis of the phases of pandemic emergency as defined by the ACS as follows[19,41,42]: Phase 1 (semi-urgent): COVID-19 patients are in the hospital, but resources and ICU beds/ventilators are not threatened; phase 2 (urgent): many COVID-19 patients are in the hospital, ICU beds/ventilator availability is strained, and operative and/or PPE resources are limited; and phase 3 (emergent): a crisis situation where most ICU/ventilator resources are directed to COVID-19 patients and operating room and/or personal protection equipment are minimally or entirely unavailable. In phase 1, the SSO suggests considering ablation or liver-directed therapies for HCC to safely delay surgery to a more stable time. However, low-grade bleeding tumours that cannot be managed with interventional radiology, radiation, or endoscopy become “cases to be done as soon as feasible”. In phase 2 and phase 3, in “hepatobiliary cancers” as a whole, alternative strategies, such as upfront chemotherapy or upfront radiation therapy, should be considered for tumours in which they are not routine, and liver-directed therapy should be considered a bridge to surgery[43].

According to the SAGES-AHPBA recommendations, during phase 1 hepatectomy, transplantation, and ablation should be pursued for HCC, while during phase 2 and phase 3, delaying definitive therapy and TACE ablation or observation are recommended[41].

Recommendations for the management of HCC and intrahepatic cholangiocarcinoma during the COVID-19 pandemic have also been released from a panel of experts belonging to different continents[9]. Specialists were invited to provide their recommendations on the management of HCC staged by the Barcelona Clinic Liver Cancer (BCLC) classification system. For patients with BCLC 0 or BCLC A, if liver transplantation or surgical resection is not feasible, the panel advocates bridging with locoregional treatments such as radiofrequency ablation, microwave ablation, stereotactic body radiotherapy, proton beam therapy, TACE, or TARE. Additionally, surveillance (*i.e.*, blood tests, such as AFP in secreting tumours, every 1-3 mo and diagnostic imaging every 3 mo), can be considered in selected cases. It should be recognized that BCLC B stage HCC involves a very heterogeneous subgroup of patients where various approaches (including surgical resection and liver transplantation in selected cases) are available according to single-institutional inclusion criteria. For patients with BCLC B stage tumours, the panel considers locoregional therapies, radiotherapy and surveillance, while for those with BCLC C stage tumours, the panel suggests the following: systemic therapy or a combination of TACE and radiotherapy (45 Gy in 15 fractions); for HCC associated with portal vein thrombosis, stereotactic body radiotherapy or TARE; best supportive care; and palliative radiotherapy in a single 8 Gy fraction for symptomatic disease[9].

In summary, hepatic resection should be performed in patients with HCC provided that standards of care are maintained in COVID-free institutions. When hepatic resection cannot be carried out because of restrictions in care delivery related to pandemic emergency, evidence from the current recommendations is in favour of the postponement of hepatic resection for those patients in whom a delay does not hamper the oncological outcome provided that a strict follow-up is warranted. Ablative or arterial-directed therapy can be performed as a definitive treatment or a bridging treatment until surgery can be performed.

ROLE OF LAPAROSCOPY

Concerns have been raised regarding the possible aerosol dissemination of SARS-CoV-2 through laparoscopic surgery[10,14,41]. In a cross-sectional survey, the European-African HepatoPancreato-Biliary Association (E-AHPBA) investigated the impact of the COVID-19 pandemic on the management of hepatobiliary-pancreatic cancers

considered as a whole. The authors examined in a survey, among other aspects, the use of laparoscopy during the pandemic. Twenty-three percent of respondents reported that laparoscopic surgery continued for both essential and non-essential cases, 58% reported that surgery continued for essential cases only, and 19% reported a suspension of laparoscopy procedures[13]. The use of minimally invasive surgery during the pandemic may have some advantages, such as a decreased length of stay, reduced postoperative complications, and, in general, less need for medical treatments[10,44]. Some authors, when an indication for hepatic resection has been established, prefer a laparoscopic approach because of advantages in respiratory function and length of stay in the hospital[38]. However, these benefits should be balanced with the potential risks of pneumoperitoneum, which is inevitable in laparoscopic and robotic surgeries and may increase the risk of aerosol exposure to the surgical and anaesthesiologist staff[10]. It is of paramount importance that all staff in the operating room wear adequate personal protective equipment[10,38]. The SAGES and European Association for Endoscopic Surgery (EAES) recommendations regarding the surgical response to the COVID-19 crisis, in theme of practical measures for laparoscopy, state that “Incisions for ports should be as small as possible to allow for the passage of ports but not allow for leakage around ports”; “CO₂ insufflation pressure should be kept to a minimum and an ultra-filtration (smoke evacuation system or filtration) should be used, if available; and “All pneumoperitoneum should be safely evacuated *via* a filtration system before closure, trocar removal, specimen extraction or conversion to open”[45].

LIVER TRANSPLANTATION

The COVID-19 outbreak has affected liver transplantation programmes worldwide, especially in communities where the incidence of COVID-19 is high and resources required for transplant activities, such as ICU beds, ventilators, and blood products, are limited[3]. In the United States, the Centers for Medicare and Medicaid Services consider transplant surgery Tier 3b category (“do not postpone”), and despite an initial decrease in liver transplantations at the beginning of the COVID-19 pandemic, liver transplant volumes have returned to 2019 levels[20]. However, liver transplant units around the world have significantly reduced their activity and revisited their protocols to select patients in whom mortality could be increased in case of a transplant delay[10,46]. The United Network for Organ Sharing reported a significant reduction in both living and deceased donor liver transplants as well as an increase in waiting-list inactivation because of COVID-19-related issues and a noticeable decline in the recovery of deceased-donor organs[47].

The evaluation for liver transplantation should be continued during the COVID era, keeping in mind that some transplant programmes might experience prolonged waiting times, especially those involving organ transplants from living donors. The major guidelines are in favour of a temporary suspension of elective living donor transplant with the aim of protecting both the potential donor and recipient[35]. According to the European Association for the Study of the Liver (EASL) position paper, living-donor transplants should be considered on a case-by-case basis[48]. It is recommended that donors and recipients be tested for SARS-CoV-2 before transplantation. In general, centres have been called to modify their usual transplant protocols according to specific priorities and local organizations[10,46,48].

Based on current recommendations, liver transplantation should not be delayed for high-priority HCC patients who have a poor prognosis in the short term, such as those with either acute or chronic liver failure, a high MELD score and HCC at the upper limits of the Milan criteria[20, 40,46,49,50]. When transplantation cannot be delayed, patients with the highest chance of cure should be selected, such as those with a single tumour < 3 cm[35]. In patients within the lower limits of the Milan criteria with compensated liver disease, liver transplantation can be rationally postponed to minimize the risks of the donor and the recipient. Moreover, in patients on transplant lists in whom a complete response to bridging therapy is observed, transplantation may also be delayed[10,23].

Alternative/holding therapy, such as ablation, bridging TAE or TACE, bridging SBRT, and bridging systemic therapy, can also be proposed in patients in whom postponing transplantation is necessary, with the exception of systemic treatment with checkpoint inhibition due to the risk of rejection[35].

Concerns about the effects of immunosuppression in transplant recipients have been raised during the COVID-19 pandemic[9,20]. In this regard, studies have shown

that immunosuppression may not be linked to an increased risk for severe COVID-19[51,52], although immunosuppressed individuals have higher viral titres than immunocompetent individuals. This aspect represents an issue to consider mostly in hospitals with a high prevalence of COVID-19[53]. According to the EASL and APASL guidelines, immunosuppressive therapy should be managed with standard immunosuppression protocols, except under special circumstances after consultation with a specialist[10,48]. In particular, a reduction in immunosuppression may be considered in patients diagnosed with moderate COVID-19 infection, lymphopenia, fever, or worsening pneumonia[10]. Liver transplant recipients should receive a vaccination against influenza and pneumococcal infection[10]. Although little is known about the effects of COVID-19 on liver transplant recipients, current evidence suggests that the severity of SARS-CoV-2 infection may be no worse in transplant patients than in non-transplant patients[54]. Given that knowledge of the risk of transmission from donors is limited, most societies suggest avoiding organs from COVID-19-positive donors[55].

INCREASING ROLE OF PERCUTANEOUS ABLATIVE TREATMENTS

In the last decade, there has been a surge in percutaneous image-guided ablation procedures for hepatobiliary-pancreatic cancers. Different ablative methods have been initially used for palliative purposes or for the local control of inoperable cases. Among them, radiofrequency ablation has been the most commonly used for the treatment of HCC. However, microwave ablation has also been gaining importance in this context[38,56,57]. With the refinements of techniques and achievement of satisfying oncologic outcomes, indications for ablative methods have expanded so that they can be used with curative intent in selected patients with HCC, such as those with very early (BCLC-0) or early (BCLC-A) HCC who are not candidates for liver resection or transplantation. However, the oncological outcomes of HCC ablation should be considered with caution when compared to hepatic resection.

In times of the COVID-19 pandemic, current recommendations suggest that radiofrequency or microwave ablation, when indicated with curative intent in patients with early HCC, can be postponed whenever possible[28,48]. If ablation is planned, patients with the highest chance of cure (*i.e.*, those with a single tumour < 3 cm) and at a low risk of developing complications should be selected[28,48].

The newest recommendations consider ablation as an acceptable alternative or bridging treatment in cases where surgery cannot be warranted in a timely manner due to the limitations linked to the COVID-19 pandemic. In particular, ablation can be considered an alternative/holding therapy for poor surgical candidates, such as those with a high risk of decompensation and comorbidities that increase the risk of severe COVID-19[35]. Santambrogio *et al*[38] suggested that ablation treatment be preferred to hepatic resection for HCCs < 3 cm in the COVID-19 era. In fact, compared to hepatic resection, liver ablation is usually a shorter procedure, with a shorter hospital stay and fewer complications[58]. According to the ASL guidelines, ablation is an acceptable alternative to resection for patients with three or fewer tumours, each 3 cm or smaller, and with Child–Pugh class A or B liver dysfunction[10,48].

In the current scenario, the ablation of HCC represents an outstanding resource as a bridging procedure in all patients in whom delaying hepatic resection or transplantation may hamper survival outcomes. Percutaneous ablation can be performed under local or general anaesthesia and can be easily repeated for either recurrence or local tumour progression. While ablation presents some important advantages as an upfront treatment for HCC in the COVID-19 era, it should be restricted to patients in whom locoregional treatment should not be postponed, and it should possibly be reserved for selected patients with the highest chance of cure. Notably, recent reports showed that patients undergoing ablation without subsequent resection, in the case of HCC recurrence, can be considered for salvage resection or salvage transplantation with outcomes similar to those undergoing upfront transplantation[59]. As a general rule, ablation represents a reasonable treatment option for patients with HCC, but its outcomes are optimized in patients with small tumours[26]. It is plausible that the surge in HCC ablation during the COVID-19 emergency will give impetus to further research on the use of this approach in patients with liver cancers in the near future.

TRANSARTERIAL BRIDGING THERAPIES

Transarterial embolization and TACE have been used for years in the management of advanced HCC. In particular, TACE, along with molecular targeted therapy, still represents the mainstay of treatment in patients with BCLC B tumours. Nonetheless, TACE remains a palliative treatment to best obtain cytoreduction, with the main goal being to control the tumour as long as possible. TACE is usually performed as an inpatient procedure, and thermal ablation should be postponed whenever possible, especially in patients at risk of decompensation or comorbidities that increase the risk of severe COVID-19[10]. Interestingly, TACE and transarterial therapies were recently proposed for patients with resectable BCLC stage HCC whose surgical procedures were cancelled. If TACE or other transarterial therapies are performed, APASL experts suggest that selective or superselective chemoembolization be attempted to prevent severe postembolization symptoms[10]. If TACE is used as a strategy to delay surgery, resection should eventually follow to avoid compromising survival outcomes[16].

BRIDGING SYSTEMIC TREATMENT

Some of the current recommendations for the management of HCC have included the possibility of administering systemic therapy as bridging systemic therapy[23,27,35]. The use of systemic therapy in patients with early HCC deserves some reflection. While neoadjuvant chemotherapy may represent an acceptable option for safely postponing surgical intervention in various cancers, it should be recognized that for patients with small HCC, there are no effective preoperative chemotherapy protocols[14,26,38,60]. This implies that a lack of a response to chemotherapy would inevitably cause disease progression and may result in non-resectability. Moreover, the diversion of operable cases towards chemotherapy could result in immunosuppression.

The tyrosine kinase inhibitor sorafenib is used in patients with Child A cirrhosis and unresectable or metastatic HCC. However, sorafenib yields stable disease at best and is not considered effective as a downstaging agent to facilitate surgical resection or as a bridging therapy to transplantation[9]. Similarly, lenvatinib and other tyrosine kinase inhibitors and vascular endothelial growth factors demonstrated efficacy against HCC, with a median OS of 12-13 mo[61], but to date, none have been investigated in the neoadjuvant setting[26]. Recent data showing responses to lenvatinib might open new applications for the use of systemic therapy in the setting of HCC patient candidates to surgery in the near future[16]. According to Japanese recommendations, systemic therapy (preferably lenvatinib) should be considered for TACE-unsuitable patients (*i.e.*, those with HCC of the extranodular growth type, confluent multinodular type, poorly differentiated type, *etc.*). In summary, in patients in whom surgery is delayed due to the COVID-19 emergency, locoregional delaying strategies should be pursued. Most likely, the use of oral systemic therapies as a bridge to a more definitive therapy may be considered only in situations where no access to locoregional therapies and surgery is possible, taking into account that disease progression may occur[16].

MANAGEMENT OF HCC IN PATIENTS WITH SARS-COV-2 INFECTION

The management of HCC patients who develop a COVID-19 infection remains ill defined, and also depends on the underlying liver disease. In fact, cirrhotic patients with COVID-19 infection may have a poor outcome for either respiratory complications or liver failure[38]. Management also varies between symptomatic and asymptomatic patients. In patients with symptomatic SARS-CoV-2 infection, the intensive treatment of the coronavirus infection overweighs that of any co-existing hepatic disease. There is a general agreement that patients with HCC and asymptomatic COVID-19 infection should postpone their surgical treatment of HCC until COVID-19 test becomes negative. Patients with suspected HCC who require tumour biopsy should postpone the procedure until at least 14 d after the onset of symptoms and when fever or respiratory symptoms have been absent for at least 3 d[28]. Also endoscopic procedures, usually performed in the preoperative work up of patients with HCC, should be postponed because spreading of virus-containing droplets can occur. Indications for endoscopic procedures in patients with COVID-19 should be limited to emergencies such as gastrointestinal bleeding, bacterial cholangitis or other life-threatening conditions[48].

CONCLUSION

Ideally, the diagnosis and treatment of HCC should not be modified because of the COVID-19 pandemic, and the management protocols should not diverge from non-pandemic circumstances. In fact, HCC is highly malignant, and delays in curative treatments, such as surgical resection and liver transplantation, heavily impact survival outcomes[10,48]. The SSO recommends hepatobiliary-pancreatic malignancies as a whole to undergo urgent operations due to the biologically aggressive nature of these cancers[43]. Similarly, the EASL stated that care of HCC should be maintained according to guidelines[48]. However, surgery for HCC is high risk and particularly resource intensive; therefore, guidelines on its surgical management should be adapted based on the pandemic emergency to perform procedures that guarantee low occupancy of the operating room, fast hospital discharge, a low rate of complications, and avoidance of SARS-CoV-2 infection.

Some kind of triage and prioritization are necessary in a period when economic and human resources are insufficient for all to be promptly treated[10,38]. Risk stratification models, mostly including the MELD score, the risk of liver decompensation, and tumour progression, are warranted to identify patients who need to be evaluated for both hepatic resection and transplantation during the COVID-19 pandemic[20]. All guidelines warrant multidisciplinary team discussions to consider patient- and tumour-specific information to propose the best strategy for each individual case.

The ILCA, French Association for the Study of the Liver, and JAMTT-HCC working groups have suggested to maintain curative treatments for HCC in COVID-19-free institutions[2,23,35]. This is probably one of the most useful measures to avoid nosocomial infection, especially for situations in which liver transplantation is warranted for the cure of HCC. At the present time, this approach remains barely reliable due to the continuous conversion of surgical and medicine wards to COVID-19 care units. However, in view of a gradual return to normal, the identification of HPB units in COVID-19-free hospitals might be the best option for patients necessitating curative intervention for HCC.

Massive vaccination campaigns against COVID-19 have been initiated worldwide since the end of 2020. At the time this manuscript was written, due to an initial limited supply of the vaccine, only patients in certain high-risk categories were allowed to be vaccinated, such as healthcare providers and older people. It is uncertain how long it will take for the COVID-19 vaccine to be distributed across the global population. While it is undebatable that vaccination is crucial to improve protection against the virus, many aspects still remain to be elucidated. Some issues regard the vaccination itself (such as its effectiveness in all individuals, potential differences in efficacy among the available COVID-19 vaccines, and the duration of vaccine-induced immunity), while others regard general vaccine campaign regulations (such as equal distribution in high- and low-income countries, the opportunity to use the same vaccination criteria in all countries worldwide, and data exchange).

Epidemiological models suggest that new waves of COVID-19 will occur before effective vaccines and therapies become available for all countries and populations[23]. Thus, it is plausible that restrictions in the surgical care of patients with HCC will extend through 2021, although progressive efforts will continue to gradually return to the pre-COVID standards of care.

Many authors have suggested using risk models or biomarkers to identify patients at the highest risk of HCC to prioritize treatments[27,62]. In fact, HCC is a heterogeneous disease, and risk stratification models may be used to identify those with the highest probability of tumour progression. To date, most models have undergone limited validation, so their clinical utility in routine practice is still limited. Nonetheless, in a restricted resource environment such as in the COVID-19 pandemic, stratification systems may be used to identify patients who can be prioritized for surveillance and those in whom surgical or ablative treatment can be delayed[62].

In the current scenario of the COVID-19 pandemic, an effort should be made to tailor management based on the available resources of the centres. Indications for the surgical resection of HCC or liver transplantation should be shared with patients and decided on a case-by-case basis, balancing the increased risk of coronavirus infection, the urgency of the intervention, and the oncological effects of the delayed treatment. To date, the present article represents the most updated review on available recommendations on the surgical treatment of HCC. These recommendations are essentially based on an expert consensus, as definitive data on the real effects of COVID-19 on HCC are not yet available. However, they may be useful as a reference for best practices in the clinical setting, with adaptation based on the trend of pandemic and categorization according to COVID-19 prevalence.

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