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Editorial Board Member of *World Journal of Gastroenterology*, Paola De Nardi, MD, FASCRS, Doctor, Surgeon, Surgical Oncologist, Division of Gastrointestinal Surgery, IRCCS San Raffaele Scientific Institute, via Olgettina 60, Milan 20132, Italy. denardi.paola@hsr.it

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Worldwide management of hepatocellular carcinoma during the COVID-19 pandemic

Riccardo Inchingolo, Fabrizio Acquafredda, Michele Tedeschi, Letizia Laera, Gianmarco Surico, Alessia Surgo, Alba Fiorentino, Stavros Spiliopoulos, Nicola de'Angelis, Riccardo Memeo

ORCID number: Riccardo Inchingolo 0000-0002-0253-5936; Fabrizio Acquafredda 0000-0002-8601-7537; Michele Tedeschi 0000-0002-2101-5418; Letizia Laera 0000-0003-2183-8817; Gianmarco Surico 0000-0002-8329-0204; Alessia Surgo 0000-0003-4502-9635; Alba Fiorentino 0000-0003-4201-5852; Stavros Spiliopoulos 0000-0003-1860-0568; Nicola de'Angelis 0000-0002-1211-4916; Riccardo Memeo 0000-0002-1668-932X.

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Riccardo Inchingolo, Fabrizio Acquafredda, Department of Interventional Radiology Unit, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70021, Bari, Italy

Michele Tedeschi, Riccardo Memeo, Unit of Hepato-Pancreatic-Biliary Surgery, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70124, Bari, Italy

Letizia Laera, Gianmarco Surico, Department of Oncology, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70021, Bari, Italy

Alessia Surgo, Alba Fiorentino, Department of Radiation Oncology, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70021, Bari, Italy

Stavros Spiliopoulos, Department of 2nd Radiology, National and Kapodistrian University of Athens, Athens 12461, Greece

Nicola de'Angelis, Unit of Minimally Invasive and Robotic Digestive Surgery, "F. Miulli" General Regional Hospital, Acquaviva delle Fonti 70021, Bari, Italy

Corresponding author: Riccardo Inchingolo, MD, Chief Doctor, Director, Department of Interventional Radiology Unit, "F. Miulli" General Regional Hospital, Strada Prov. 127 Acquaviva-Santeramo, Acquaviva delle Fonti 70021, Bari, Italy. riccardoin@hotmail.it

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has impacted hospital organization, with the necessity to quickly react to face the pandemic. The management of the oncological patient has been modified by necessity due to different allocation of nurses and doctors, requiring new strategies to guarantee the correct assistance to the patients. Hepatocellular carcinoma, considered as one of the most aggressive types of liver cancer, has also required a different management during this period in order to optimize the management of patients at risk for and with this cancer. The aim of this document is to review recommendations on hepatocellular carcinoma surveillance and management, including surgery, liver transplantation, interventional radiology, oncology, and radiotherapy. Publications and guidelines from the main scientific societies worldwide regarding the management of hepatocellular carcinoma during the COVID-19 pandemic were reviewed.

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Core Tip: Hepatocellular carcinoma is one of the most common cancers in the world. The aim of this review is to focus on the impact of the coronavirus disease 2019 pandemic on the management of patients with hepatocellular carcinoma and to verify how multidisciplinary management has changed to face the necessity of hospital reorganization.

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INTRODUCTION

In December 2019, the world experienced a new coronavirus from China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for a respiratory disease with the characteristics of a worsening interstitial pneumonia, later called coronavirus disease 2019 (COVID-19). This virus spread quickly across all continents generating a global pandemic, officially declared on March 11, 2020, which has put hospitals around the world under pressure as they were unprepared to face a very high number of hospitalizations in intensive care units and medical wards[1]. This affected not only intensive care, but clinical services of cancer patients as well. In fact, the recruitment of a large part of medical staff in the aforementioned departments in order to contain and fight this new health emergency caused serious problems in the management of all other wards with consequent delays in the care and surveillance of patients with other pathologies and, in particular, of those with oncological disease[2,3]. Moreover, cancer patients are at major risk to contract COVID-19 infection both from nosocomial exposure and due to their immunocompromised states [4].

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world, which accounts for approximately 6% of all cancer incidences[5] and is nowadays considered a global health problem[6]. Compared to other neoplasms, HCC patients are more susceptible to the effects of the COVID-19 pandemic because the hepatic injury[7] caused by SARS-CoV-2 could complicate the pre-existing hepatitis virus infection and cirrhosis in most HCC patients.

Due to the major treatment limitations and exposure risk created by the pandemic for patients with HCC, a general consensus amongst clinicians acknowledged that deviations from the standard of care are necessary, and specific international guidelines on HCC management have been drafted by the American Association for the Study of Liver Disease[8], the European Association for the Study of the Liver[9], the International Liver Cancer Association[10], the Asian Pacific Association for the study of the Liver[11], and the São Paulo Clínicas Liver Cancer Group Multidisciplinary Consensus Statement[12] (Table 1).

The aim of this review is to compare and summarize all these recommendations and guidelines, particularly in the diagnostic and therapeutic process of patients affected by HCC to provide clinicians with the best measures to be adopted in the framework of this ongoing pandemic.

SURVEILLANCE

As recommended by the American Association for the Study of Liver Disease and the European Association for the Study of the Liver, deferring HCC surveillance by 2–3 mo during the COVID-19 pandemic because of reduced radiologic capacity is likely

Table 1 Recommendations from main international liver society

	APASL	HC-FMUSP	EASL-ESCMID	ILCA	AASLD
Liver resection	Generally, liver resection with curative intent should not be delayed. However, in cases of high risk of decompensation or comorbidities, surgical intervention should be postponed or alternative therapy such as ablation should be adapted	The indications for surgical resection are the same as those during the pre-pandemic period and are as follows (18-21): In patients without cirrhosis: Solitary or oligonodular HCCs; in patients with chronic liver disease: Solitary tumors (regardless of size), preserved liver function (Child-Pugh A), and absent or mild portal hypertension (small caliber esophageal varices and platelets 100000/mm ³)			Can consider bridging locoregional therapy (TACE/TARE/SBRT), systemic therapy, or active monitoring if necessary to delay surgery
LT	LT for patients with poor short-term prognosis should not be delayed. Elective living donor transplantation may be suspended. In patients with complete response to bridging therapy on transplant list, transplantation may be suspended	LT is the treatment of choice for patients with early HCC (BCLC-A) and impaired liver function (Child-Pugh B/C), clinically significant portal hypertension, and those with early HCC who are not candidates for resection	Patients on the LT waiting list with decompensated cirrhosis are at high risk of severe COVID-19 and death following SARS-CoV-2 infection. We therefore recommend that LT centers aim to restore transplantation services following the peak of the COVID-19 epidemic wherever possible. In centers with ongoing resource limitations, LT should be prioritized for patients with poor short-term prognosis including those with acute liver failure, ACLF, high MELD score (including exceptional MELD points), and HCC at the upper limits of the Milan criteria	Unique considerations of COVID-donor derived infection and immunosuppression post-transplant. Consider cessation of LDLT (lower MELD) and delaying transplant in those with complete response	Limit the number of patients coming to clinic for transplant evaluations. Consider evaluating only patients with HCC or those patients with severe disease and high MELD scores who are likely to benefit from immediate liver transplant listing
Ablation	Ablation with curative intent should not be delayed. Ablation is an acceptable alternative to resection for cases of three or fewer tumors, each 3 cm or smaller, and of Child-Pugh class A or B liver dysfunction	Radiofrequency ablation can be performed in patients with very early (BCLC-0) or early (BCLC-A) HCC and have solitary nodules < 3 cm in size			Reserve for those with best chance of response (size < 3 cm) and can consider SBRT
Vascular intervention	Vascular interventions may be postponed because they are used as cytoreductive treatments in most cases. Vascular interventions should be suspended in cases of risk of decompensation or comorbidities that increase the risk of severe COVID-19	TACE/TAE: Can be performed in patients with solitary nodules > 3 cm in size as local disease control or as a "bridge treatment" to surgery			Consider TACE for single or multifocal HCC. Consider TAE, DEB-TACE or TARE instead of TACE and perhaps systemic therapy in some patients with large tumor burden
Radiation therapy	Radiation therapy for cases of symptom control or at low risk of progression may be postponed. However, radiation therapy for function- or life-threatening situations have to be treated without delay. The course of radiation	SBRT: Can be considered in patients who have contraindications to RFA or TACE/TAE			

	should be shortened when appropriate	
Systemic therapy	Oral tyrosine kinase inhibitors would be better than infusion regimens during the pandemic. The impact of immunotherapy on the course of COVID-19 is not known	Systemic therapy: May be used as a “bridge therapy” for surgery in patients with contraindications to other treatments

ILCA: International Liver Cancer Association; AASLD: American Association for the Study of Liver Disease; SBRT: Stereotactic body radiation therapy; COVID-19: Coronavirus disease 2019; TACE/TAE: Transarterial chemoembolization/embolization; LT: Liver transplantation; HCC: Hepatocellular carcinoma; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; LDLT: Living donor liver transplantation; MELD: Model for end-stage liver disease; ACLF: Acute-on-chronic liver failure; EASL-ESCMID: European Association for the Study of the Liver-European Society of Clinical Microbiology and Infectious Diseases; APASL: Asian-Pacific Association for the Study of the Liver society; RFA: Radio frequency ablation; TARE: Transarterial radioembolization; BCLC: Barcelona Clinic Liver Cancer; DEB-TACE: Drug-eluting bead transarterial chemoembolization; HC-FMUSP: São Paulo Clinicas Liver Cancer Group Multidisciplinary Consensus Statement.

safe. In patients with active COVID-19 infection, HCC surveillance should be postponed until they recover[13].

Although surveillance is important for early detection of HCC, risk varies between patients; in an environment with limited resources, risk stratification models[14-16] may be used even if they have not been fully clinically validated. This can be useful to identify patients who need to be prioritized for surveillance.

If ultrasound-based surveillance is not possible for extended periods of time because of lack of social distancing between operator and patient, blood-based biomarkers may be considered as an alternative strategy. Given the insufficient sensitivity and specificity of alpha-fetoprotein used alone[17], different biomarker panels have been proposed. The best evaluated is GALAD, which combines gender, age, and three biomarkers (alpha-fetoprotein, alpha-fetoprotein-lectin-reactive, and des-gamma carboxyprothrombin)[18].

HCC surveillance after curative therapy (surgery and ablation) is recommended and should be performed using cross-sectional imaging with multiphase abdominal computed tomography or contrast enhanced magnetic resonance imaging, the latter associated with noncontrast chest computed tomography[19].

A principle of maximizing the risk-benefit ratio should be taken for the surveillance of HCC and monitoring of patients who have received therapies for HCC. Prioritizing imaging resources to those patients at highest risk of incident HCC and recurrence following therapy, while prioritizing those patients who are eligible for an imminent liver transplantation (LT) is a judicious strategy to risk stratifying these patients.

INTERVENTIONAL RADIOLOGY

During the outbreak of the COVID-19 pandemic in early 2020, serious restrictions were applied in interventional radiology (IR) departments regarding the management of elective procedures. Resources and facilities were diverted to treat the large number of COVID patients, allowing limited opportunities for non-COVID-19 related procedures. Primarily urgent/emergency and carefully selected elective cases were performed in IR departments. This largely affected IR cancer care worldwide[20]. More specifically, for patients with HCC where meticulous coordination between different specialties and sequential various IR treatments (mainly percutaneous ablation and different types of transarterial embolotherapy) followed by strict imaging follow-up protocols are required to maintain an efficient therapy. The pandemic caused significant disturbances and negatively affected patient care[7].

There is consensus that HCC patients should continue to receive locoregional therapy during the COVID-19 pandemic, with choice of therapy discussed in a multidisciplinary format[8]. There is concern for serious COVID-19 infection in those receiving conventional transarterial chemoembolization (TACE) (with cytotoxic agents) because of systemic absorption with increased myelosuppression, and therefore the International Liver Cancer Association recommends other forms of locoregional therapy over conventional TACE (*e.g.*, bland embolization, drug-eluting bead-TACE, Y-90)[10]. Finally, consideration for earlier transition to systemic therapy could be considered in locally advanced HCC patients[21].

Several authors investigated the effect of the pandemic in HCC patients. In a study published by an Italian center, the authors reported that clinical practice adapted to minimize HCC patient exposure to the virus. As a result, a delay of treatment (transarterial procedures, thermal ablation, and systemic treatment) of ≥ 2 mo was noted in 26% of the patients during the COVID-19 outbreak compared with the same period in 2019[22]. Similarly, in a French multicentric study investigating patients from six referral centers of the metropolitan area of Paris (an area highly impacted by the COVID-19 pandemic), 21.5% of patients experienced a treatment delay > 1 mo in 2020 compared to 9.5% in 2019 ($P < 0.001$), although a significant difference in the modification in treatment strategy between the two periods was not noted[23]. Nevertheless, the impact of the COVID-19 pandemic on IR treatment outcomes in patients with HCC remains to be determined.

Generally, experts recommend avoiding treatment delays in HCC patients in order to decrease the risk of tumor progression, while patients with the highest chance for definite cure and those with the lower risk of developing severe complications should be prioritized for treatment. In an elegant review of current evidence, Chan *et al*[7] stratified the modifications of treatment required for HCC patients according to the stage of the disease[7]. The authors summarized that all patients should undergo multidisciplinary team evaluation using stricter selective criteria in order to identify those who would benefit the most from IR therapy. Optimally, patients could be referred in centers where IR services were less affected by the pandemic. In early-stage HCC, ablation was advised over surgical resection due to the limited availability of operating rooms, intensive care unit beds, and anesthetic facilities. In intermediate-stage HCC, TACE patient selection to identify patients that will benefit more could be performed using specific stratification scores, such as the Barcelona Clinic Liver Cancer (BCLC) stage B subclassification, the hepatoma arterial-embolization prognostic score, and the “beyond-up-to-seven” criteria. A personalized decision should be then taken regarding the number and frequency of TACE sessions, while in cases in which TACE therapy could not be appropriately followed due to unacceptable delays, systemic treatment or regular surveillance could be alternatively used.

SURGERY

Several guidelines have been proposed to clarify how to maintain standard of care of HCC in this pandemic era.

According to the European Association for the Study of the Liver- European Society of Clinical Microbiology and Infectious Diseases, listing for transplantation should be restricted to patients with poor short-term prognosis including those with acute/acute-on-chronic liver failure, high model for end-stage liver disease score (including exceptional model for end-stage liver disease scores), and HCC at the upper limits of the Milan criteria because transplantation activities/organ donations will likely be reduced in many countries and areas.

For patients already listed, SARS-CoV-2 routine testing should be performed before LT in both donors and recipients. Living-donor transplantations should be considered on a case-by-case basis. After LT, guidelines should be followed as usual trying to avoid as much contact as possible with medical staff.

In HCC patients, care should be maintained according to guidelines, including treatment and evaluation for LT[9].

A paper from the Italian Association of the Study of the Liver stated that the management of HCC has been negatively affected by the pandemic with, unfortunately, a reduction of surveillance and follow-up. Particularly, surgical procedures had been reduced or suspended in 44% of the centers. COVID-19 has also affected the liver transplant activity with a reduction in the number of performed transplants in 23% of the centers and interruption of the activity in less than 1%[24].

A multidisciplinary evaluation has been proposed by Santambrogio *et al*[25] with a treatment strategy adapted to the tumor size. Particularly, HCC less than 2 cm should be followed up monthly, those between 2 cm and 3 cm should be preferentially treated by local ablation (percutaneous or laparoscopic), while HCC > 3 cm require a surgical approach, preferably avoiding major hepatectomies and using the laparoscopic approach[25]. The Asian-Pacific Association for the Study of the Liver Society proposes that liver resection with curative intent should not be delayed. However, in cases of high risk of decompensation or comorbidities that increase risk of severe COVID-19, surgical intervention should be postponed or alternative therapy such as ablation should be adapted. Laparoscopic or robotic surgery during the pandemic may

contribute to decreased length of stay as compared with open surgery as well as minimizing the need for medical treatments. On the other hand, pneumoperitoneum, which is inevitable in laparoscopic or robotic surgery, may bring a higher risk of aerosol exposure to the surgeons and staff.

Transplantation should be decided on case-by-case basis. LT for patients with poor short-term prognosis, such as with high model for end-stage liver disease score and HCC at the upper limits of the Milan criteria are in high priority and should not be delayed. Those with compensated liver disease and within the lower limits of Milan criteria have medium priority and may be suspended to minimize the risk of the donor and the recipient. In patients with complete response to bridging therapy on the transplant list, transplantation may also be suspended until it can be performed safely with sufficient resources[11].

The International Liver Cancer Association suggests that surgical treatment should be offered to patients with low risk of decompensation and without comorbidities that increase the risk of severe COVID-19. If surgery is not possible, then alternative strategies should be performed (local ablation, TACE)[10].

The policy formulated by The Working Group Report of the Japan Association of Molecular Targeted Therapy for HCC recommends that 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 *vs* radiofrequency ablation trial indicate that radio frequency ablation, the less invasive option, should be proactively considered if there are \leq three nodules each measuring \leq 3 cm, which would shorten hospital stay[26]. 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[27].

The São Paulo Clínicas Liver Cancer Group Multidisciplinary guidelines state that surgery should be considered for patients with chronic liver disease and solitary tumors > 3 cm in size, to preserve liver function, with no clinically significant portal hypertension or other comorbidities, who are young, and with favorable locations for resection. This multidisciplinary group agrees with others that the living donor liver transplant program should be temporarily suspended in order to preserve both donors and recipients.

They also consider delaying LT in patients with a complete response to “bridge therapies” and maintain close monitoring with imaging examinations to detect any recurrence. Patients with HCC who have significant liver dysfunction and/or viable tumors and have a high risk of losing eligibility for transplantation, especially those who do not respond to “bridge therapies” or present with tumor progression, should remain on the list for LT[12].

ONCOLOGY

During the COVID-19 pandemic, the medical community is experiencing a crisis due to lack of resources. But cancer patients represent a heterogeneous group that differ in prognosis, progression, and treatment. Oncologists have an important role to play for their patients in regard to resource reallocation[28]. In this era, the oncological approach to HCC treatment has been modified. Since February 2020, the first analysis related to SARS-CoV-2 infection patients demonstrated a higher risk of mortality between patients with cancer. The risk is due to the cancer but also to age, smoking history, and comorbidities[29]. In addition, patients with liver cancer appear to be more vulnerable because of underlying liver disease that can alternate both innate and adaptive immune responses[30].

The systemic treatment in advanced HCC (BCLC-C patients/Child Pugh-A liver function) is generally with multitargeted tyrosine kinase inhibitors characterized by daily oral administration (*e.g.*, lenvatinib, sorafenib). Not all countries have approved the combination of immune check point inhibitors and the antiangiogenic agent bevacizumab[31] with an intravenous administration. Oral tyrosine kinase inhibitors should be preferred over an infusion regimen during the pandemic to protect both patients and medical staff. The role of immunotherapy in SARS-CoV-2 infection is unknown. The use should be considered on a case-by-case basis[11].

In accord to the international and national guidelines during the COVID-19 pandemic, the telemedicine approach must be preferred[9,10]. Some recommendations suggest to rank in person patient visits as high, medium, and low priority. For

example, high priority patients are taking first and following line therapies, patients showing moderate or severe side effects to treatment, or with decompensated liver disease. In any case, a phone assessment is preferred[32].

If systemic therapy is ongoing, the use of telephone-based consultations should be preferred, enabling careful monitoring of patients without the need for frequent hospital visits over a short period of time[27]. The recommendation is to reduce the access in the hospital for a visit and improve telephone-based assessment with clinical evaluation and blood tests. In the case of in person visits, a phone call the day before the appointment should be made to consider the patients' general condition and the presence of any suspected symptoms (for example fever or rhinorrhea). In addition, at the hospital entrance temperature should be measured, hands should be disinfected, and the patients should be alone. Related to less complicated toxicities, such as hypertension, dermatological problems, and diarrhea, the management can be performed by community doctors after coordination with the patient's team[7].

For liver cancer clinical trials, regular visits should be maintained[33].

These modifications for clinical daily practice should be taken to reduce the risk of SARS-CoV-2 infection in patients with advanced HCC undergoing systemic treatment.

RADIOTHERAPY

During the COVID-19 pandemic, new guidelines have been introduced for the management of oncological treatments in radiotherapy (RT) departments[34,35].

Cancer patients are known to have a higher degree of fragility and therefore are inclined to complications of COVID-19 infection. Therefore, an appropriate risk-benefit assessment of each procedure should be considered as part of the treatment strategies for cancer patients during the pandemic[36].

RT is one of the cancer weapons, reporting a benefit in terms of overall survival and disease-free survival. By the introduction of advances in RT, providing high precision delivery while sparing at-risk organs, it is generally well tolerated with a median overall treatment time of 20-30 daily fraction. Furthermore, the use of hypofractionation or stereotactic RT treatments (SBRT) with few fractions (about 1-15) is preferred during the pandemic to reduce access times in hospitals.

In this context, SBRT treatment has a role as a noninvasive and effective therapy, for patients with HCC from the early stages to the most advanced stages. In general, the total dose on the tumor was 30-60 Gy in 3-5 fractions[34].

In early stage HCC, local therapy can be offered as a bridging treatment if surgery would be postponed or as a definitive therapy in the context of locoregional treatments, in the case of the inability to perform surgery[12,34].

In the case of intermediate stage HCC, SBRT has been proposed as an alternative option, particularly after an incomplete response to the previous TACE or for patients unfit for TACE[37]. Finally, in the case of locally advanced HCC with vascular invasion, RT with TACE has been shown to improve survival compared to TACE alone in patients with HCC[38]. In patients with advanced disease, the use of SBRT can reduce the time of suspension of systemic therapy if the patient requires palliative therapies to control symptoms derived from the disease[11,12,34].

In addition, the collaboration between 19 multidisciplinary liver specialists from high-volume liver malignancy academic centers in seven countries and five continents has resulted in a series of recommendations regarding the management of HCC patients in the era of COVID-19. According to the BCLC classification system, it is evident that RT and SBRT treatments are actively included in every stage of HCC[39].

When standard therapies are not available these recommendations can be considered: (1) BCLC-0 or BCLC-A: if a liver transplant or surgical resection is unavailable, consider bridging with locoregional therapies or surveillance. In this case SBRT 30-60 Gy/3-5 fractions; (2) BCLC-B: consider locoregional therapies, such as TACE, transarterial embolization, transarterial radioembolization, or SBRT 30-60 Gy/3-5 fractions or surveillance; and (3) BCLC-C: if patient has portal vein thrombosis and no extrahepatic disease, consider systemic therapy or a combination of TACE and radiotherapy (45 Gy in 15 fractions), SBRT in 3-5 fractions, or transarterial radioembolization; if patient has extrahepatic disease, use systemic therapy and/or palliative radiotherapy in a single 8 Gy fraction for symptomatic disease[12].

Using SBRT hospital access times are reduced compared to using standard fractionated or hypofractionated treatments (a max of six treatments for SBRT compared to fifteen or more in the other cases). Furthermore, the recommendations during the pandemic require the use of noninvasive immobilization systems, such as

active breathing and motion control management (breath-hold techniques, respiratory gating, abdominal compression) or free breathing treatment, according to the possibilities of each radiotherapy department, to mitigate respiratory movements avoiding the surgical implantation of liver fiducial markers during radiotherapy simulation phase and treatment.

It is fundamental for accurate triage to identify positive or suspected cases before and during treatment, and if the patient should test positive for SARS-CoV-2 during radiation therapy, then they may consider treatment suspension or the continuation of the same in a protected environment both in consideration of the patient's clinical condition and treatment purpose and in relation to the situation of each center to ensure a safe radiation treatment[36].

It is known, despite numerous phase II prospective and retrospective studies demonstrating SBRT safety and efficacy[40,41], that most guidelines in the management of patients with HCC limit the use of RT to patients who are not suitable or refractory to other locoregional treatments due to the lack of phase III trials. However, as discussed in the literature[42], it is anticipated that with more widespread clinical use of SBRT during the COVID-19 pandemic and the result of ongoing trials, there may be increased evidence to support the effectiveness of SBRT for HCC treatment.

CONCLUSION

The COVID-19 pandemic has strongly impacted the management of the oncological patient due to the reduction of inpatient beds and reallocation of nurses and doctors to the COVID departments that were rapidly developed in each hospital to face the pandemic. Despite this unexpected reorganization of hospitals, the necessity to continue to manage patients with HCC has required the continuation of multidisciplinary management while reducing the risk of COVID-19 negatively affecting the short and long-term oncological outcome. The main goals should be to optimize the risk/benefit balance and focus on patients with a more aggressive tumor. Flexibility has become mandatory in order to adapt to the different phases of the pandemic. The aim of these guidelines is to prepare physicians to manage the second and third wave of the COVID-19 pandemic.

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