Impact and the delivery of loco-regional treatment for hepatocellular carcinoma during the COVID-19 pandemic

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ABSTRACT

Hepatocellular carcinoma (HCC) is the second most lethal tumour, with therapies broadly divided into curative and palliative intent. Unfortunately, the majority of HCCs were found to be unresectable at diagnosis. Advances in novel loco-regional therapies have given patients with unresectable HCC a vital chance for disease control and survival. However, the COVID-19 pandemic has greatly shaped and impacted treatment protocols and delivery for HCC patients. This review article aims to describe the impact of the COVID-19 pandemic on the delivery of loco-regional treatment modalities for HCC and compare treatment trends between the pre-pandemic and pandemic eras. Treatment of HCC involves complex collaboration between clinical professionals within their local and global healthcare institutions. The COVID-19 pandemic has had a profound impact on the treatment of HCC. The delivery of loco-regional treatment for HCC will need to adapt to each healthcare system’s unique structure.

1. Introduction

Hepatocellular carcinoma (HCC) is an aggressive primary hepatic malignancy with a predilection for individuals with chronic hepatic disease and cirrhosis. As the second most lethal tumor after pancreatic cancer, population studies revealed a 5-year survival of 18%. Treatment for HCC can be broadly divided into curative or noncurative therapies. Curative therapies aim to achieve complete disease eradication, while those of noncurative intent focus on delaying tumor progression. Surgical intervention constitutes the mainstay of curative therapy for localized HCC. However, tumor spread or existing hepatic dysfunction curtails these surgical efforts. Unfortunately, in the Western populations, only an estimated 5–10% of HCC tumors are amenable to resection at diagnosis. The advent of novel loco-regional treatment protocols provides patients with unresectable HCC a vital alternative for disease control and survival prolongation.

On 31st December 2019, the World Health Organization was notified of a cluster of viral pneumonia cases of an unknown causative organism. At the time of writing, this virulent strain has infected more than 576 million individuals and killed an estimated 6.4 million patients. The novel Coronavirus, named Coronavirus Disease 2019 (COVID-19), has impacted all facets of healthcare delivery and patient care. The restrictions imposed on elective procedures hope to strike a delicate balance between reining in the spread of COVID-19, providing optimal patient care and healthcare resource allocation. Elective interventional radiology procedures saw a broad reduction in numbers compared to the pre-pandemic era. These changes resonated with various societal guidelines published by both interventional radiology and surgical institutions. However, given the heterogeneity of the disease characteristics of HCC compounded by the dynamic state of the COVID-19 pandemic across nations, institutions struggle to conclusively provide recommendations for the treatment of HCC. While the indications for surgical resection of HCC have been well described, loco-regional treatments often performed by interventional radiologists cover an array of modalities and therapeutic possibilities.

This review article focuses on the delivery of loco-regional treatment modalities for HCC during the COVID-19 pandemic and contrasts treatment trends pre-COVID and during the pandemic.

2. COVID-19 and cancers

Multiple cohort studies and analyses have been performed to study the impact this pandemic has on cancer patients, documenting the devastating impact this pandemic has on cancer patients. In a systematic review of 62 studies by Riera et al., authors found a multitude of delays and disruptions to healthcare delivery to cancer patients during the pandemic. These ranged from logistical limitations in healthcare supplies and manpower to a reduction in clinic and treatment availabilities. A

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meta-analysis by Saini et al. evaluated the case fatality rate of patients with both COVID-19 and cancers. Fifty-two research studies were included, totaling 18,650 patients afflicted by both diseases. A 25.6% probability of death (95% CI: 22.0%–29.5%; 12 = 48.9%) was noted in this patient cohort. While no comparison was made with the pre-pandemic era, this sheds light on the staggering impact this infection can have on cancer patients. In China, a meta-analysis involving 38 studies and 7094 patients concluded that cancer patients infected with COVID-19 were significantly associated with severe events of COVID-19 (odds ratio = 2.20, 95% CI [1.53, 3.17]; P < .001) and mortality (odds ratio = 2.97, 95% CI [1.48, 5.96]; P = .002). These studies reveal just how devastating the pandemic has been and continues to be for patients infected with malignant neoplasms.

To our best knowledge, no studies have been published on the effects of COVID-19 vaccines on primary hepatic malignancies. Hwang et al. described the possible benefits and risks of inoculating cancer patients with the COVID-19 vaccine. The study provides a broad overview of all COVID-19 vaccines currently approved for use or late in development. This ranged from inactivated virus vaccines to mRNA vaccines. While no conclusive data is available on the safety and benefits of COVID-19 vaccination in cancer patients, the authors conclude that vaccination’s advantages likely outweigh possible risks.17 This recommendation concurs with that proposed by Kuderer et al., who recommended prompt vaccination of patients with cancer, given the greater risk for morbidity and mortality of COVID-19 infection in these patients. However, the authors highlighted the need for further research to shed light on vaccination timing relative to patients’ cancer treatment and possible immunosuppression.18

3. COVID-19 and liver disease

An estimated 1.5 billion people worldwide are infected with chronic hepatic disease.19 The COVID-19 virus is not only associated with hepatic injury and dysfunction, but the presence of hepatic functional deficit could increase susceptibility to this virus. Wu et al. performed a meta-analysis on the impact of COVID-19 on liver dysfunction and found a significant correlation between hepatic dysfunction and mortality of COVID-19 (pooled odds ratio = 1.98, 95% CI 1.39–2.82; P = .002).20 Merola et al. found a 22.17% (95% CI 17.64 to 27.07) pooled prevalence of COVID-19 related hepatic damage through a meta-analysis of 11 studies. The findings of COVID-19 related hepatic damage are echoed in a meta-analysis by Li et al., which reported a 25% overall prevalence of liver injury in COVID-19 patients. In March 2021, a meta-analysis by Singh et al. performed analysis on array-based gene expression datasets and found upregulation of genes commonly involved in COVID-19 infection in patients with non-alcoholic fatty liver disease. This raises the concern of increased susceptibility of COVID-19 infection in this subset of patients.24

4. COVID-19 and hepatocellular carcinoma

A review of the current literature reveals a dearth of research specifically describing the influence this pandemic has on patients with HCC and the management of this malignancy. Many notable institutions propose that the care of HCC patients should mirror that of the pre-pandemic era. At the point of writing, no new guidelines have been published by the American Association for the Study of Liver Diseases or the European Association for the Study of the Liver tailored to the COVID-19 pandemic.25,26 In 2020, members of the Asian Pacific Association for the Study of the Liver published guidelines on the optimal clinical management of HCC. The expert panel concluded that the diagnosis and treatment of this highly-malignant disease should not be delayed and should parallel the pre-pandemic era. This recommendation is consistent with the American College of Surgeons Elective Surgery Acuity Scale, which provides a framework for triaging various diseases amenable to surgery, whereby HCC may be classified as a “Tier 3a (high acuity)” disease and treatment should not be delayed. However, the authors also recognize the logistical and medical challenges faced by institutions in providing care.

In April 2020, the International Liver Cancer Association (ILCA) published a guidance document on the possible issues and holistic care of patients with HCC during the pandemic.26 The organization addresses the need for possible deviations from the current standard of care as part of a temporizing measure until definitive care can be provided, as institutions ration healthcare resources.

An international committee involving 19 multidisciplinary liver specialists led by Barry et al. documented guidelines for managing primary hepatic malignancies during the pandemic era.29 Patients were triaged according to the BCLC classification system for hepatocellular carcinoma. In Brazil, members of the S Black Liver Cancer Group also published guidelines to standardize the management of HCC patients during this pandemic. The authors recommended a multidisciplinary approach to provide prompt workup and treatment for patients suspected of or diagnosed with HCC.

In summary, experts internationally concur in the need for early diagnosis and treatment of HCC similar to the pre-pandemic era, given the prospect of cancer spread and concomitant liver disease. While a multidisciplinary approach to this disease is paramount, they also recognize the varying impacts the pandemic has on different specialties in providing care and the need to adapt to local pandemic situations.

5. COVID-19 and delivery of loco-regional therapy for hepatocellular carcinoma

Loco-regional treatment for HCC can be broadly classified into ablative and transarterial techniques. Ablative procedures consist of radiofrequency ablation, microwave ablation, percutaneous ethanol or acetic acid ablation, and cryoablation. The two main types of transarterial therapies include chemoembolization and radioembolization. Various international oncological organizations have proposed guidelines on the application of loco-regional treatment for HCC. The Barcelona Clinic Liver Cancer (BCLC) classification system for HCC proposed by Llovet et al., in 1999, and updated subsequently, provides a framework for staging HCC and recommends evidence-based therapies for patients at each stage. In general, curative treatment is recommended in early-stage HCC (stages 0 and A), encompassing surgery, hepatic transplantation, and ablation. For intermediate stage HCC, palliation with transarterial therapies is proposed. This emphasizes the breadth of treatment options Interventional Radiology offers for patients with HCC.

Interventional Radiology and the provision of loco-regional therapies for HCC patients comprise a resource and manpower-intensive process for optimal care delivery. The COVID-19 pandemic challenges these efforts in treating our patients.

Various guidelines for procedural prioritization and postponement have been published, such as the Procedure Acuity Scale by the Society of Interventional Radiology and American Association for the Study of Liver Diseases. In our institution, while logistical and procedural adjustments were made to cope with the pandemic, various strategies to maintain operational load were employed to defer delay in cases, allowing for a similar volume of cases being performed during the pre-pandemic period and during the pandemic (Fig. 1). To minimize inpatient footprint and infection risk, transarterial treatment for intermediate-stage HCC was primarily performed on an outpatient basis in our center. To minimize physician movement and potential cross-institutional infections, we also trialed the use of telemedicine as part of multidisciplinary care for patients receiving Yttrium-90 (Y-90), allowing for continued collaboration with off-site Nuclear Medicine specialists. Guidelines on the employment of telemedicine in the field of Nuclear Medicine have also been previously crafted by the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine. To reduce patient movement and hospital resources for multiple admissions, same-day Y90 radioembolization for HCC has also been performed in our
institution. The practice of same-day angiography, 99mTc-MAA scintigraphy, and 90Y radioembolization not only translates to a reduced risk of potential COVID-19 spread by reducing patient movement but has also shown to provide more expeditious cancer care.\textsuperscript{39,40}

Other than impacting intra-hospital processes, COVID-19 also has far-reaching impacts on many elements beyond the healthcare institution. Edge et al. evaluated the psychological impact the pandemic had on cancer patients and carers in Australia. The study revealed the multifaceted consequences the pandemic has on individuals in aspects such as psychological distress, cancer service disruptions, and carer issues.\textsuperscript{43}

With lockdowns imposed on many nations, delivery delays and cessation of crucial medical supplies such as Y-90 microspheres also had a devastating impact on healthcare delivery for HCC patients. This situation is encapsulated in a study by Bhaskar et al.\textsuperscript{41} The authors describe the collapse of the global supply chain for medical supplies during the pandemic and stress the pressing need for more robust logistical systems in addressing global healthcare needs in preparation for future pandemics.

In conclusion, the impact of the CODI-19 pandemic is well recognized and has profound effects on patients with HCC. The delivery of locoregional treatment for HCC needs to be tailored for patients and their existing healthcare systems.

Declaration of competing interest

The authors have no relationships with industry stakeholders, conflicts of interest and financial disclosures to declare.

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