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Influence of the COVID-19 pandemic in the gastrointestinal oncology setting: An overview

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been impacting healthcare in various ways worldwide and cancer patients are greatly affected by the coronavirus disease 2019 (COVID-19) pandemic. The reorganization of the health facilities in order to supply the high demand resulting from the aforementioned infection as well as the social isolation measures led to impairments for the diagnosis and follow-up of patients with gastrointestinal cancers, which has had an impact on the prognosis of the oncologic patients. In that context, health authorities and organizations have elaborated new guidelines with specific recommendations for the management of individuals with gastrointestinal neoplasms during the pandemic. Of note, oncologic populations seem to be more susceptible to unfavorable outcomes when exposed to SARS-CoV-2 infection and some interactions involving virus, tumor, host immune system and anticancer therapies are probably related to the poorer prognosis observed in those COVID-19 patients. Moreover, vaccination stands out as the main prevention method against severe SARS-CoV-2 infection and some particularities have been observed regarding the seroconversion of vaccinated oncologic patients including those with gastrointestinal malignancies. In this minireview, we gather updated information regarding the influence of the pandemic in the diagnosis of gastrointestinal neoplasms, new recommendations for the management of gastrointestinal cancer patients, the occurrence of SARS-CoV-2 infection in those individuals and the scenario of the vaccination against

the virus in that population.

Key Words: Gastrointestinal cancer; COVID-19; Treatment; Diagnosis; Vaccination; Pandemic

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Core Tip: The coronavirus disease 2019 pandemic has impacted the care of patients with serious chronic conditions such as cancer. In this minireview, we gather updated information regarding the influence of the pandemic in the diagnosis of gastrointestinal neoplasms, new recommendations for the management of gastrointestinal cancer patients, the occurrence of severe acute respiratory syndrome coronavirus 2 infection in those individuals and the scenario of the vaccination against the virus in that population.

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak emerged in 2019 which soon spread worldwide becoming a pandemic[1]. Coronavirus disease 2019 (COVID-19) infection is one of the greatest threats to global public health and by March 2022 the World Health Organization had already identified 464809377 confirmed cases and 6062536 deaths[2]. The course of the disease ranges from asymptomatic to fatal infection and its clinical presentation is mainly characterized by respiratory symptoms such as cough and dyspnea but it can also affect other systems leading to cardiac, gastrointestinal, renal, neurological, cutaneous and hematological disorders[3]. Severe COVID-19 primarily affects patients with comorbidities including individuals with cancer who are often immunocompromised[4]. Gastrointestinal neoplasms including colorectal, gastric, liver, esophageal and pancreatic cancers are relatively frequent and some of them are among the malignancies that kill the most in the world, such as gastric and colorectal cancers[5]. In the context of the new coronavirus pandemic, tumors that affect the gastrointestinal tract are the most common malignancies among patients infected with COVID-19 in various investigations[6]. Disturbingly, SARS-Cov-2 infection in oncologic patients is linked to higher rates of intensive care unit (ICU) admission, greater need for mechanical ventilation and increased propensity to death[7-9].

The clinical practice of oncologists and the routine of cancer patients were significantly affected by the effects of the COVID-19 pandemic[10]. The measures adopted to prevent the spread of the disease and the overload of health services around the world impacted the diagnosis of some malignancies, especially those that require invasive procedures such as colorectal and gastric cancers[11]. In addition, cancer health care including oncologic surgeries, visits to the health system, outpatient consultations and anti-cancer therapies were negatively affected by experiencing delays or interruptions during treatment[12]. Finally, vaccination is the main available strategy to prevent the SARS-CoV-2 infection. However, studies have highlighted particularities involving the effectiveness of the available immunizers in the oncologic population[13-15].

This minireview focuses on addressing the key challenges faced by oncologists and patients with gastrointestinal malignancies in face of the changes that follow the aforementioned pandemic. The aim is to highlight the main aspects discussed in the current scientific evidence regarding diagnosis, treatment, vaccination and infection prevention among patients with gastrointestinal cancer in that context.

METHODS

In order to review the repercussions of SARS-CoV-2 infection in patients with gastrointestinal cancer, a search was performed for relevant articles published in English in the National Library of Medicine (PubMed) database until March 5, 2022. In this sense, two researchers acted independently using the following descriptors: COVID-19; SARS-CoV-2 in combination with Gastrointestinal cancer; Gastric cancer; Esophageal cancer; Colorectal Cancer; Treatment; Cancer diagnosis; Vaccination. The selection of studies was made by screening the titles and abstracts of articles. We included studies that evaluated

outpatients and inpatients with confirmed SARS-CoV-2 infection who had cancer, outpatients and inpatients with confirmed SARS-CoV-2 infection who had gastrointestinal cancer, prospective, retrospective, cross-sectional studies, systematic reviews and narratives.

IMPACTS OF THE COVID-19 PANDEMIC OVER GASTROINTESTINAL CANCER DIAGNOSIS

Healthcare systems around the world have been broadly impacted by the COVID-19 pandemic. Many health facilities had to be reorganized in order to uphold the high demand for medical assistance imposed by the aforementioned disease[16]. Financial, structural and personal resources have been redirected to supply the unexpected consequences that follow such an unprecedented health problem [17]. Other issues also impaired the access of populations to healthcare providers including the burden of the pandemic over the economy as well as the difficulties and fears faced by populations to reach healthcare centers in the presence of lockdowns and other measures for contagion containment[18]. In addition, the interruption of nonurgent medical procedures, including diagnostic tests, in order to avoid viral dissemination, was another trouble in that setting[19]. Unfortunately, these changes undoubtedly prejudiced the proper assistance and early diagnosis of serious chronic conditions such as gastrointestinal malignancies.

A population-based study performed by Maringe *et al*[20] in England aimed at estimating the influence of the pandemic over cancer deaths due to delays in diagnosis in that country, gathering 24975 individuals with colorectal cancer and 6744 persons with esophageal malignancy. They estimated an increase of about 15.3%-16.6% in the number of colorectal cancer-related deaths and an enhancement of 5.8%-6.0% in esophageal cancer-associated deaths within the first 5 years after diagnosis. Another study carried out with the Chilean population estimated the impact of the COVID-19 outbreak on the diagnosis and survival of breast, cervix, colorectal, prostate and stomach cancers. The results predicted a larger percentage of individuals diagnosed with cancer at advanced stages between 2020 and 2022 which leads to a lower 5-year net survival. They prevised 3542 extra deaths from 2022 to 2030 (95% UI 2236–4816) associated with these cancers, led by colorectal cancer, which accounts for 1389 excess deaths (95% UI 364–2567), whereas stomach cancer will probably be the cause of 6.0% of those additional deaths[21].

In addition, an investigation performed in an academic health center in New York (United States) compared the number of diagnostic and resection specimens for the detection of gastrointestinal malignancies during the years 2018, 2019 and 2020. They included 949 patients, gathering 1028 pathology samples, and observed a reduction of 57% in the number of samples in 2020 compared to the preceding year ($P < 0.01$). Moreover, a drop in the number of colorectal cancer specimens from older patients was found when pre- and post-COVID-19 periods were compared ($P < 0.01$)[22]. Alarmingly, a retrospective Japanese study evaluated 5167 patients (4218 before the pandemic and 949 diagnosed with gastrointestinal cancer during the pandemic) and observed that during the pandemic period there was a significant decrease in diagnoses of stage 0 colorectal cancers ($P = 0.008$, stage I ($P = 0.003$) and stage II (0.01) and an increase in diagnoses in stage III malignancies ($P < 0.001$)[11]. These data evidence the repercussions of the pandemic on the diagnosis of gastrointestinal cancers as well as the impact of the delay for diagnosis on the prognosis of oncologic patients. Interestingly, a study with 298 patients carried out in an Italian hospital observed a lower number of elective colorectal cancer screening colonoscopies, but a higher detection of colorectal cancer cases during the pandemic[23]. They found five cases (8%) of the malignancy among individuals ($n = 60$) evaluated from March 9 to May 4, 2020 (lockdown group), and only 3 cases (1%) among the patients ($n = 238$) who underwent the diagnostic assessment in the same period of 2019 (control group, $P < 0.01$). Moreover, the prevalence of patients with more high-risk factors for the disease, such as a familiar positive history and significant symptoms (*e.g.*, rectal bleeding), was higher in the lockdown group. These results suggest that the presence of meaningful risk factors for colorectal cancer probably made patients prioritize the diagnosis of the disease despite the risk of acquiring SARS-CoV-2 infection.

TREATMENT OF GASTROINTESTINAL CANCER PATIENTS DURING THE PANDEMIC

Since the World Health Organization declared the SARS-CoV-2 outbreak a pandemic, the impacts of the infectious disease on cancer treatment have become a major concern around the world. Patient protection and continuity of treatment became challenging factors within that context in which social isolation and reduced displacement were the main measures to be taken.

In Europe, one of the first continents that became the epicenter of transmission, health authorities and governments decided to postpone consultations for patients with gastric cancer or carry them out remotely, treatment plans were reformulated and many clinical trials on gastrointestinal malignancies had their development impaired. In Italy and the United Kingdom (UK), for example, some health units

were designated for the exclusive care of patients with COVID-19 and others to assist individuals without the infection, and even so it is estimated that more than 200000 weekly exams were unable to be performed in the UK[24].

In a Japanese cross-sectional study carried out with 61 patients undergoing treatment for gastrointestinal cancer, it was observed that the pandemic caused a reduction in the number of exits and more caution regarding the prevention of infections ($P < 0.001$) as well as an increase in the occurrence of anxiety and insomnia in those patients during treatment ($P < 0.01$). Of note, most patients do not wish to change their treatment plans as recommended by guidelines developed during the pandemics[25] and this may be due to the fear and insecurity in face of the chance of having a worse prognosis because of a decrease in the frequency of care measures. Another American study that compared 25666 patients being treated for gastrointestinal cancer in 2020 and 23530 patients followed up in 2019, observed that there were statistically significant decreases in the number of radiotherapies and surgeries in patients with gastrointestinal neoplasms[26]. Sozutek *et al*[27] recently observed a reduction of about 70% in the volume of cases of colorectal cancer at an academic center during the pandemic. This study also showed that there was a lower proportion of cancer resections ($P = 0.01$), with a decrease of about 15% in the number of colorectal cancer surgical therapies ($P = 0.04$)[22]. These results indicate that the pandemic, indeed, has had negative impacts on the treatment of patients with various gastrointestinal malignancies.

The international survey in question focused on the preoperative screening of asymptomatic patients aiming to elucidate the current global situation of surgical practice under the COVID-19 pandemic. A total of 936 centers in 71 countries completed the survey; the survey respondents were a total of 1173 surgeons who represented the centers' surgical departments. Results show that the majority of them (73.8 per cent) performed preoperative COVID-19 testing exclusively based on symptoms or suspicious radiologic findings, but only 22.8 per cent of the overall centers performed routine screening by chest-computer tomography (CT) scan. To test every surgical patient for COVID-19 was a guideline recommended in barely 17 per cent of the centers. Results also show that 27.5 percent of the centers reported asymptomatic COVID-19 patients who tested positive postoperatively; most centers (81.9 per cent), only then, changed testing policies and preventive measures in surgical practice[28].

The surgeon's personal feelings were also investigated in the survey; in total, 1124 surgeons replied to the questions. When asked about the personal fear of getting sick or infecting others, the respondents overall reported a relatively high score of 37 ± 13 , 1 point meaning "never" and 5 points meaning "always". Just over 50 per cent of the surgeon's said to be satisfied with the hospital's preventive measures, agreeing that their centers were taking enough preventive measures to avoid in-hospital transmission. The survey clarified the current surgeons' fear of getting infected was particularly associated with shortage of gloves, gown, hand sanitizer and medical masks. That, in addition to experiencing in-hospital infection, which was reported in 31.5% of the overall centers and the majority of these centers failed to trace it. Social support for the surgeons' fear and secure working environment with enough personal protective equipment (PPE) supply have shown to be unwarranted[29].

Despite all the risks involved in performing surgical procedures during the pandemic, a 60-d observational study of 177 patients with gastrointestinal cancer observed that there was no SARS-CoV-2 infection in any staff member or patient who underwent tumor resection during the study period. They concluded that even in a hospital that takes care of patients with COVID-19, if there are adequate prevention measures for both the patients and the medical staff, the procedure can be performed safely, thus optimizing the treatment of these patients[27]. It is important to point out that, unfortunately, this was not the reality of most underdeveloped countries which had little availability of adequate infrastructure and resources for the implementation of proper preventive methods to avoid SARS-CoV-2 contagion and had to postpone many surgical procedures due to the high chance of infection in a hospital environment[30].

While a guideline for clinicians published by the World Health Organization states that patients who have confirmed COVID-19 infection should be assessed for holding anticancer therapy until they are deemed medically clear, it is unquestionable that surgery and adjuvant therapies cannot always be postponed; emergency surgery is still recommended in certain diagnoses[31]. Studies show that patients who underwent chemotherapy or surgery in the past month before diagnosis with COVID-19 had a higher risk of severe clinical events than those not receiving chemotherapy or surgery. Therefore, the necessity of any interventional procedure must be balanced against the increased risk during a pandemic and should be evaluated on a case-by-case basis[9,32]. The potential benefit of chemotherapy remains unchanged during a pandemic, but the risk of harm would be increased to a degree that cannot be quantified. Undoubtedly, cancer patients need to be made aware that myelosuppressive treatment could carry greater risk during a pandemic so they may well make an informed choice[31,33]. Moreover, it is clear that an intentional postponement of adjuvant chemotherapy or elective surgery for stable cancer should be considered for patients with acute SARS-CoV-2 or other infections[32].

However, delays for surgery or curative adjuvant chemotherapy can only be considered within acceptable periods for each disease. While some cases can be postponed indefinitely, the majority of them are associated with progressive diseases that will continue to advance at variable disease-specific rates. For instance, while some asymptomatic breast cancer tumors can be followed up until the pandemic is more controlled or over, chemotherapies against stage III colorectal cancers can only be

safely delayed up to 8 wk post -surgery, but more than 12 wk of delay is not recommended, being associated with worse outcomes[34,35].

To spare this group of patients the possibly irreparable consequences of delayed treatment in this uncertain pandemic setting, it is imperative that each hospital should review its own facilities and provide these patients with treatment when possible. During the COVID-19 pandemic, one of the points to be considered when making the decision for surgery in cancer patients is the current condition of the hospital. Operating rooms are high-risk areas for contact contamination through airway or possible splash; to avoid the risk is it a demand that they should be very well-designed to deal with this type of high contamination risk situation; a minimum number of people should enter and leave patient rooms for all types of work and procedures. The widespread use of hand washing, antiseptic procedures and PPE should be ensured by the hospital and usage rules should be strictly followed. In cases of required emergency surgery for a patient with both cancer and ongoing SARS-CoV-2 infection, it has to previously be defined in detail the operational, perioperative and postoperative management including prevention and control measures for the medical staff, operating rooms and surgical tools as well as the protection of the wards, healthcare personnel and other patients. Hospital resources should be evaluated with a multidisciplinary approach and a personalized treatment protocol should be developed for each patient[36-38].

Considerations for gastric and esophageal cancer

Upper gastrointestinal tract (esophageal and gastric) malignancies rank among the ten most common malignancies worldwide while gastric cancer still remains one of the leading causes of cancer-associated deaths. The incidence of upper GI malignancies varies widely and regions with high COVID-19 incidence such as, China, Japan, Central, and South America, also represent areas with the highest occurrence of esophageal and non-cardiac gastric cancer[39].

With regard to the treatment of these malignancies, the Society of Surgical Oncology affirms that most upper gastrointestinal tract cancer surgeries are not elective. If there are inadequate resources to manage potential complications then surgery may need to be delayed or, if necessary, referred to centers with resources to perform the procedure. Discussion of cases remains critical to assert priorities, resources, and personalized treatment plans based on the hospital, patient and tumor specificities. However, a few organ-specific approaches are determined: cT1a lesions amenable to endoscopic resection may preferentially undergo endoscopic management where resources are available; cT1b cancers should be resected; cT2 or higher and node-positive tumors should be treated with neoadjuvant systemic therapy. Given the concerns regarding laparoscopic surgery in COVID-19 patients, since the SARS-CoV-2 may be present in the smoke caused by the cautery devices, consideration may be given to proceeding straight to neoadjuvant treatment in COVID-19 positive patients.

Patients completing neoadjuvant chemotherapy may stay on chemotherapy if responding to and tolerating treatment. If patients are not responding to systemic treatment, resection and/or referral may be considered. Patients with gastric outlet obstruction or hemorrhage should be treated with endoscopic measures to allow for enteral nutrition or control of bleeding; proceed to surgery if these measures fail. In less biologically aggressive cancers, such as gastrointestinal stromal tumors - unless symptomatic or bleeding - surgery may be considered for short-term deferral[40].

Considerations for colorectal cancer

Guidelines have been published by several associations based on the experience gained from colorectal cancer patients in China and Italy, during the pandemic, reciting recommendations to protect both patients undergoing cancer treatments and healthcare professionals. These guidelines all converge to a general direction: It is critical to postpone elective surgery as much as possible but to perform emergency surgery provided that general measures are taken. The Society of American Gastrointestinal and Endoscopic Surgeons published similar guidelines recommending that surgical intervention should be performed in cancer patients who are likely to progress or who require emergency intervention. The situation is not all that simple with regard to colorectal cancers. It is accepted that surgery should be performed in life-threatening conditions such as cancer patients with perforating, obstructing, actively bleeding tumors or septic patients, but other conditions might require further consideration such as looking into the status of the patient, the stage of the tumor, the risk of the surgical procedure and the condition of the respective hospital[41]. Asymptomatic stage I-II patients can have their elective colon cancer surgery deferred for 30 d and have a new decision made at the end of this period; they will not be affected unfavorably by the deferral up to approximately 6 wk. However, the need for a further deferral at the end of the 60-d-period warrants radiological staging for decision making in those patients. In asymptomatic stage III colon cancer patients, deferral longer than 30 d should involve discussing a plan of neoadjuvant chemotherapy. In asymptomatic stage IV colon cancer patients, guidelines recommend initiating chemotherapy and planning surgery depending on the radiological response after three courses of chemotherapy[42]. **Figure 1** summarizes the recommended approach to colon cancer in the context of COVID-19.

Rectal surgery can wait no longer than 60 d between the diagnosis and the treatment or the rate of survival will be considerably lower. In a stage I asymptomatic rectal cancer, a 30-d deferral might not affect the oncological outcomes. At the end of the 30-d delay, depending on the patient's symptoms,

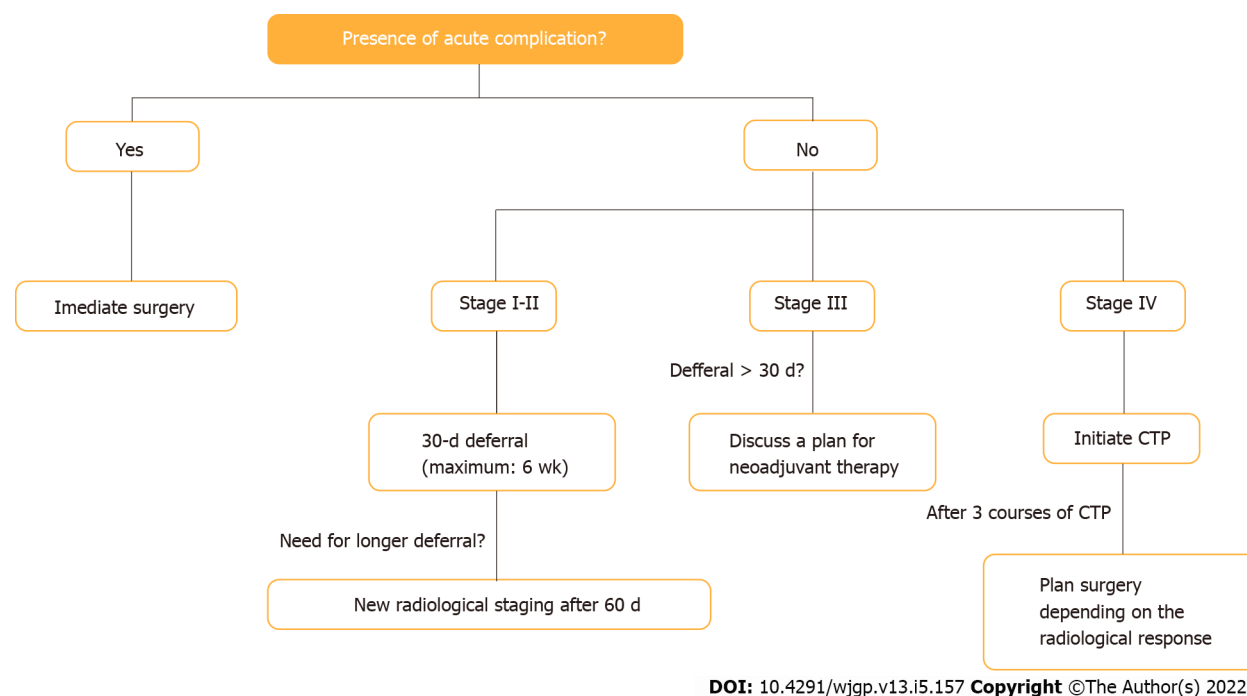


Figure 1 Summarizes the recommended approach to colon cancer in the context of coronavirus disease 2019. CTP: Chemotherapy.

treatment can be deferred for another month but radiological staging is necessary to make any new decisions. In stage II-III rectal cancers, radiotherapy should be administered; its response should be evaluated in the 8th week after radiotherapy. If there is a regression with radiotherapy, surgery could wait for a period of up to 12 or even 16 wk while the patient is closely monitored. If, however, results show no regression at the 8th week with radiotherapy, the decision for surgery can be made depending on the infrastructure of the hospital[43].

Symptomatic rectal cancer patients, usually between the stages II-IV, should make the decision for the treatment depending on the severity of symptoms and findings and their effect on the quality of life. Radiology staging is necessary; patients who are symptomatic but can wait, should, preferably, defer the surgery as described for asymptomatic stage I, II and III. As for patients who have been diagnosed with malignant polyps, it is appropriate to postpone prophylactic surgeries. Whichever the decision regards the patient's treatment, it is necessary to choose protocols that will minimize the patient's hospitalization for both surgery, radiotherapy and chemotherapy procedures. It is peremptory that all the staff should be careful and follow the protocols during the preoperative and postoperative period to prevent infection for themselves and all other patients hospitalized[36].

An issue that should not be forgotten is the fact that because of the aforementioned higher risk of viral transmission in laparoscopic surgeries, open surgeries are the most suitable for COVID-19 patients. If the surgery has to be performed laparoscopically, fixed pressure insufflators, a closed-circuit smoke absorption system, a negative pressure operating room and a carbon dioxide filter should be used to discharge the smoke to reduce the aerosol effects of insufflation. On the other hand, laparoscopic surgery is associated with earlier recovery and discharge and might benefit individuals who are not currently infected with the virus. In summary, minimally invasive surgery, ideally, should not be used in cases known to be infected with SARS-CoV-2 and should only be used after all necessary precautions have been taken[40].

SARS-COV-2 INFECTION AMONG PATIENTS WITH GASTROINTESTINAL CANCER

The current scientific evidence indicates that individuals with cancer might be more susceptible to a severe course of infection with SARS-CoV-2[44]. The greater likelihood of severe development is probably explained by the immunosuppression that often accompanies malignancies and oncological therapies[45]. However, data on the repercussions of SARS-Cov-2 infection in cancer patients are still being developed with the possibility of inconsistencies regarding the conclusions on the subject[46]. In addition, most studies address various types of neoplasms with a focus on lung and blood cancer, with limited information on gastrointestinal malignancies. In a case-control analysis with 73.4 million cancer patients, including colorectal cancer, the authors concluded that cancer carriers are at increased risk of SARS-CoV-2 infection and that the occurrence of the infection is associated with higher rates of hospitalization and mortality in that population. It confirms the occurrence of worse outcomes among infected

oncologic patients and, interestingly, these findings were especially substantial among African Americans[4].

Furthermore, two meta-analyses had similar conclusions regarding COVID-19 infection in cancer patients. The first included 38 studies and 7094 patients with COVID-19, with a pooled cancer prevalence of 2.3%, and demonstrated that cancer significantly contributed to the occurrence of severe course and death in SARS-CoV-2 infections. The second covered a total of 110 studies with a combined prevalence of cancer as a comorbidity of 2.6% in hospitalized patients with COVID-19 and indicated that the risk of mortality is about five times higher among oncologic patients when compared to non-elderly SARS-CoV-2-infected individuals without comorbidities[44]. One of the first cohorts on the subject evaluated characteristics and clinical outcomes of 105 individuals with gastrointestinal cancer and COVID-19 and 536 non-oncologic SARS-CoV-2-positive patients. Their findings revealed that patients with COVID-19 and gastrointestinal cancer had worse outcomes regarding mortality, ICU admissions, the prevalence of at least one severe or critical symptom and the need for invasive mechanical ventilation when compared to the non-oncologic patients[47]. In addition, a retrospective study with 52 oncologic COVID-19 patients found that some complications such as liver injury (36.5%), acute respiratory distress syndrome (17.3%), sepsis (15.4%), myocardial injury (15.4%), renal failure (7.7%) and multiple organ dysfunction syndrome (5.8%) are common in cancer patients infected with SARS-Cov-2 and, therefore, these individuals may be more prone to more severe outcomes[45].

A study looked at COVID-19-related clinical symptoms, survival rate and risk of infection among cancer patients, including colon cancer and gastric cancer, and the results suggested that thrombocytopenia, anemia and diarrhea are symptoms that increase independently the risk of death in oncologic patients with COVID-19[48]. Another study portrayed gastrointestinal manifestations in 36 cancer patients, of whom 8 had gastrointestinal cancer. Their results concluded that the most prevalent gastrointestinal symptoms in the hospitalized patients were anorexia (52%), diarrhea (39%) and vomiting (35%) and that elevations in hepatic transaminases were associated with a higher occurrence of gastrointestinal symptoms[49].

From an immunological point of view, viral infections and neoplasms are associated with high levels of proteins that activate the T cell-mediated response leading to inflammation which may play important roles in cancer progression[50]. In this sense, some signaling pathways can be affected by both COVID-19 infection and cancer, influencing the expression of type-I IFN and androgen receptor as well as the activation of immune checkpoint signaling pathways, and alterations at these points of the immune response have the potential to lead to the development of a cytokine storm that is closely associated with acute respiratory distress syndrome, organ failure and death in severe COVID-19[51]. Furthermore, ACE2 receptors are highly consumed in SARS-CoV-2 infection due to their ability to assist the virus in cell entry[52]. For this reason, there is a decrease in the availability of those receptors and, as a consequence, important functions played by these receptors may be compromised[52]. In this context, low ACE2 activity has the potential to contribute to severe inflammation and is related to some types of gastrointestinal malignancies such as gallbladder cancer and pancreatic ductal adenocarcinoma[53,54]. Another well-established issue in cancer patients is the immunosuppression caused by the depletion of leukocytes and the use of glucocorticoids in addition to other oncological therapies that compromise the ability of the immune system to respond to viral infections such as SARS-CoV-2 infection, leading to a course of more serious illness[55].

Despite what has been discussed so far, some studies present results that contrast with the conclusions that associate cancer with worse COVID-19 infection outcomes. A prospective cohort that included 9842 patients found that the incidence and severity of clinical presentation of COVID-19 infection in cancer patients are not significantly different from those observed in the general population [46]. In agreement with the aforementioned results, in an observational study gathering 78 cancer patients positive for SARS-Cov-2, only one developed the severe form of the disease and only three developed symptoms[56].

VACCINATION AGAINST COVID-19 IN GASTROINTESTINAL CANCER PATIENTS

During the new coronavirus pandemic, as soon as vaccination schemes were implemented, certain priority groups were identified, taking into account the epidemiological data obtained so far. In this sense, cancer patients were considered as a priority group, mainly, the worst prognosis of the disease among these individuals including a higher mortality rate. In this context, institutions such as the Asian Oncology Society, the European Society for Medical Oncology and the National Comprehensive Cancer Network recommended that cancer patients be a priority thus including individuals undergoing treatment or about to undergo treatment and those who underwent treatment for at least 6 mo[51,57].

However, despite the priority for vaccination, little is known about the immune response of these individuals after the application of the immunizer. It is necessary to take into account that cancer patients, including those with gastrointestinal involvement, have conditions linked to the disease and to the treatments adopted that can compromise the effective response to the vaccine. In this context, chemotherapy, by causing bone marrow suppression can cause thrombocytopenia and neutropenia. In

addition, radiotherapy, because it is capable of damaging the DNA of cells, including lymphocytes, is also capable of causing lymphopenia. Associated with this, therapies that use corticosteroids and other immunosuppressive elements can further compromise the full functioning of the immune system of individuals undergoing cancer therapy and directly influences the immune response to vaccination. In addition, the initial clinical trials did not include individuals with cancer and the literature addressing the relationship between the vaccine and cancer patients is scarce[58].

Thus, given the need to better understand the immune response to the vaccine in cancer patients, some studies were carried out bringing results with the ability to directly influence the care provided to this group. However, studies focusing exclusively on patients with gastrointestinal involvement seem to have not yet been performed.

Among the parameters adopted by the studies to analyze the immune response to vaccines, anti-Spike (anti-S) IgG antibodies were the most used. Thus, the Coronavirus Disease 2019 Antiviral Response in a Pan-tumor Immune Monitoring (CAPTURE) trial, which included 585 participants, including 87 with gastrointestinal cancer (19%), evaluated individuals immunized with the BNT162b2 (Pfizer-BioNTech) or AZD1222 vaccines (Oxford-AstraZeneca) and found 85% seroconversion after the application of two doses of the immunizer in the general group of patients with solid cancer. In addition, they reported that older age is related to a lower titer of neutralizing antibodies[59].

In this context, studies evaluating seroconversion after the application of the CORONAVAC vaccine were also carried out. In this sense, Yasin *et al*[60] defined an IgG level ≥ 50 AU/mL as seropositive in a study that included 776 cancer patients, including 174 (22.4%) with gastrointestinal involvement, and 715 non-cancer volunteers. The seropositivity rate and antibody level were significantly lower in individuals with cancer when compared to the control group ($P < 0.001$). In this context, the seropositivity rate was 85.2%, with a mean antibody titer of 363.9 AU/mL in the patient group and 97.5%, with a mean antibody titer of 656.5 AU/mL in the control group. In addition, as the CAPTURE study pointed out, age was a factor associated with a lower rate of seropositivity ($P < 0.001$). The study also pointed to ongoing chemotherapy in the group of cancer patients ($P = 0.038$) as a factor capable of negatively influencing seropositivity rates, the opposite was pointed out by the Vaccination Against COVID in Cancer (VOICE) and CAPTURE trials[61]. Table 1 summarizes the seroconversion rates of the immunizers among oncologic patients.

Another important point is linked to the increase in antibody titers that were observed after the application of the second dose. Thus, it is noted that only one dose of the immunizer provides immunity much lower than that which can be obtained with the application of two doses[62]. In this context, Becerril-Gaitan *et al*[57] reported that cancer patients with an incomplete vaccination schedule, when compared to individuals in the control group without cancer, had a 55% reduced probability of reaching anti-S IgG titers above the stipulated threshold (RR 0.45; CI95% 0.35-0.58). For those with a complete vaccination schedule, the reduced probability was 31% (RR 0.69; 95% CI 0.56-0.84).

Given the above, although individuals with cancer reach acceptable seroconversion rates, despite being reduced compared to the “healthy” population, studies indicate that the application of booster doses is indicated for individuals with compromised immunity[63,64]. Thus, in August 2021, the Food and Drug Administration (FDA) authorized the application of the booster dose to immunosuppressed individuals[13]. In this context, Ligumsky *et al*[14] when analyzing the response of 72 cancer patients and 144 “healthy” individuals (control group) to the booster dose of the BNT162b2 vaccine (Pfizer-BioNTech), they initially observed that before the application of the third dose, 20 cancer patients (28%) and two in the control group (1%) were seronegative. However, after the application of the booster dose, only three cancer patients and none of the control group remained seronegative. In addition, when comparing the absolute concentration of anti-SARS-CoV-2 S IgG antibodies, they observed that there was a significant increase in levels in both groups ($P < 0.0001$). In this context, studies also point out that the application of the booster dose can guarantee a better response to variants of concern such as Delta and Omicron[15].

Therefore, it is evident that cancer patients have a less pronounced immune response to vaccination, even with the application of the third dose, when compared to “healthy” individuals in the control group, although satisfactory in most individuals. In addition, it is noted that the application of the booster dose is capable of guaranteeing greater seroconversion in this group and therefore should be encouraged. Finally, more studies are needed to better understand the immune response of cancer patients to currently available vaccines, given that these individuals are subject to variables related to cancer and to the different treatments that can be applied which influence immunity in different ways.

Adverse effects associated with vaccination against COVID-19

Another factor that should be taken into account are the adverse events that may occur as a result of vaccination. In this sense, studies were carried out to analyze the acceptance of cancer patients to immunization. In one of these studies, which involved the participation of 364 cancer patients, when asked if they would take the vaccine as soon as it became available, 41.8% answered “yes”, 37.6% answered they were “not sure”, and 20.6% answered who would not get the vaccine. Among the factors that encourage cancer patients to be vaccinated are the fear of getting sick, trust in the recommendations of health professionals and the desire to contribute to herd immunity. As for those who expressed doubt or refusal of the vaccine, fear and concern about possible adverse effects were present in 24.5% of the

Table 1 Seroconversion of immunizers in oncologic patients

Immunizer	Ref.	Cancer patients, n	% GIC	Seroconversion, %
BNT162b2 (Pfizer–BioNTech), OR, AZD1222 (Oxford–AstraZeneca)	Fendler <i>et al</i> [59]	585	19	85
CORONAVAC	Yasin <i>et al</i> [60]	776	22.4	85.2

GIC: Gastrointestinal cancer.

participants[65].

In this sense, studies suggest that, as in the general population, cancer patients tend to have mild to moderate effects. Thus, a study that included 291 participants immunized with BNT162b2 reported adverse events following immunization in 14.78% of subjects. These include local reactions, pyrexia, fatigue, headache and chills. Furthermore, the risk of developing these events was higher in women ($P = 0.001$) and young patients ($P = 0.009$). Another study, which evaluated the BNT162b2 vaccine in 326 participants diagnosed with cancer, reported similar results, without any serious reaction[66,67].

However, despite the majority of events being mild or moderate, the possibility of serious complications exists. Thus, there are case reports that associate certain events with vaccination. In this context, Chong *et al*[68] reported severe thrombocytopenia 3 d after the application of the first dose of the Moderna vaccine and Brage *et al*[69] reported fulminant myocarditis after receiving the third dose of the Moderna vaccine. In this context, it is evident that serious adverse events can occur, but most patients have mild or moderate events. However, more studies are needed to better clarify the effects presented and understand the possible interactions between the different types of anti-cancer treatment and the epidemiological factors of each individual with the development of mild, moderate or severe reactions.

Nevertheless, it is still the role of health professionals to inform their patients about the risks and benefits of vaccination helping them to make effective decisions.

CONCLUSION

The COVID-19 pandemic has been negatively impacting the diagnosis, treatment and prognosis of gastrointestinal cancer. Although most studies indicate that having cancer, in general, implies a greater risk of severe COVID-19, it is an ongoing pandemic with still limited studies and only a few investigations are specific for neoplasms from the gastrointestinal tract. The immunosuppression caused by cancer and its related therapies probably make the patient more vulnerable to infections; however, the measures adopted to avoid the contagion in this population can also impair anticancer therapies. Therefore, it is essential that research on the subject continues to evolve towards a better understanding of how the pandemic caused by the new coronavirus interferes with the context of gastrointestinal cancer in order to improve the approach to cancer patients and solve remaining challenges in that context.

FOOTNOTES

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