



## COVID-19 in patients with gastrointestinal stromal tumors: Recommendations for management and vaccination

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### Abstract

The coronavirus disease 2019 (COVID-19) pandemic profoundly affected the management and treatment of patients with malignancies. Based on the progress reported in the literature, we reviewed the recommendations for treatment and vaccination in patients with gastrointestinal stromal tumor (GIST) during COVID-19. We focus on whether there is a risk and what could be the possible effects of vaccinating patients with GIST/cancer. Since the situation is quickly changing, and the health services have been severely disrupted, the diagnosis, treatment and recommendations for vaccination of these patients against COVID-19 are still not updated. The approval of vaccines in the pandemic gave hope that we would soon be able to return to a more normal life. However, the oncology community needs to adapt and provide the most effective treatment and care models for patients with rare cancer, such as GIST. Collecting data on the impact of

vaccination in patients with GIST/cancer also will be beneficial in expanding knowledge about the future planning of treatment strategies and optimizing care in the event of a subsequent pandemic.

**Key Words:** Gastrointestinal stromal tumor; GIST; Cancer; COVID-19 vaccination; efficacy; Treatment strategy; Side effects

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**Core Tip:** Even under normal operating conditions, appropriate monitoring and treating patients with gastrointestinal stromal tumors (GISTs) require complex decision-making. Given the growing number of deaths worldwide and the failure of many countries to control the pandemic, vaccination against COVID-19 in these patients must be accelerated. The data show no significant difference in the efficacy of vaccines for the GIST population compared to that of other cancers. Vaccination between cycles of therapy and after waiting periods for patients with stem cell transplantation and immunoglobulin therapy can be used to reduce the risks while protecting patients from risk groups.

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## INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in China at the end of 2019 and coronavirus disease 2019 (COVID-19) are considered risk factors for severe outcomes in cancer patients[1]. Statistics indicate that by March 13, 2022, there have been > 6 million deaths caused by COVID-19 worldwide, and the number of confirmed cases recorded is > 455 million[2].

In line with this, according to a number of reports, diseases such as diabetes, hypertension, cardiovascular diseases, respiratory diseases, and cancer are associated with an increased risk of fatality in patients diagnosed with COVID-19[3]. In addition, an international study involving 1035 patients with COVID-19 who have concomitant cancer showed that these patients had a higher risk of hospitalization and need for intensive care and mechanical ventilation, regardless of the type of malignancy and antitumor therapy[4].

Patients with malignant diseases represent a heterogeneous group. Therefore, it remains to be determined which factors related to tumor type and treatment increase the risk of infection with COVID-19 and adverse outcomes[5]. According to a study that aimed to identify the risk factors of severe COVID-19 infection in patients with malignancy, the administration of antitumor treatment (chemotherapy, radiotherapy, targeted therapy or immunotherapy) within 14 d of diagnosis significantly increases the risk[6].

To assist health care facilities and minimize the negative effects of the pandemic associated with COVID-19 in patients with malignancies, the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology, the National Comprehensive Cancer Network (NCCN) and other organizations have developed recommendations for patient categorization based on the Ontario Health Cancer Care criteria[7].

Gastrointestinal tumors are a relatively new tumor group that has emerged in recent decades from other mesenchymal tumors in this field, mainly neurofibromas and leiomyomas, thanks to the achievements of modern medicine in molecular biology and pharmacotherapy. Therefore, the justification for a separate tumor form merits an in-depth multidisciplinary study. Furthermore, it represents a model for successfully applying targeted therapy in treating solid tumors[8].

Gastrointestinal stromal tumors (GISTs) are rare neoplasms of the gastrointestinal tract associated with high rates of malignant transformation. They represent 1%–2% of all gastrointestinal neoplasms [9]. The mean age at diagnosis is 58 years, with most patients being between the ages of 40 and 80 years [10].

Although the risk of SARS-CoV-2 infection is not increased in GIST patients, they may experience other consequences during the COVID-19 pandemic, such as delay in treatment, delayed surgery or long waiting period for elective surgery, a heavy burden on medical resources, and the need for emergency surgery[11]. Additionally, neoadjuvant imatinib is routinely used to shrink locally advanced GISTs and if there is a danger of positive margins, unresectable, or borderline resectable tumors[12]. Imatinib may be a beneficial alternative to minimize the possibility of tumors developing in

intermediate or high-risk cancers bearing imatinib-sensitive mutations that would otherwise be excised during a time of limited access to surgical therapy[12]. Even if imatinib is generally well tolerated, patients may develop adverse effects such as myelosuppression (grade 3 in up to one-fifth of all patients), which might be concerning if the patient becomes infected with SARS-CoV-2[13]. Finally, initial watchful waiting would not rule out the possibility of starting imatinib if the tumor progressed.

The term GIST was introduced by Mazur and Clark in 1983 for a group of nonepithelial mesenchymal tumors of the gastrointestinal tract (most often leiomyomas, leiomyosarcomas and neurinomas), which differ from the eponymous tumors in other areas of the body in their immunohistochemical characteristics[14]. It is now commonly accepted that GISTs derive from so-called pacemaker cells in the intestinal tract – the interstitial cells of Cajal or similar stem cells[15]. Cajal cells are intermediates of gastrointestinal autonomic nervous system cells and smooth muscle cells and regulate the motility and autonomic nerve conduction and function activity. They are positive for Kit and Kit-ligand (stem cell marker), localized around the myenteric plexus and in the stratum muscularis propria along the entire gastrointestinal tract. Cajal cells can either be or include a subclass of multipotent, stem-like cells that can differentiate into smooth muscle cells if the Kit signaling pathway is disrupted[16]. In most cases, GISTs are specifically Kit (CD117) positive or caused by mutations in *Kit* or *PDGFRA* genes, and are the primary mesenchymal tumors of the gastrointestinal tract with characteristic histological features[17].

In the 1990s, GIST were found to express CD34 antigen, which has been identified as a distinguishing feature of neurinomas and leiomyomas. However, in a new study phase, GISTs were found to have standard immunohistochemical and ultrastructural features with Cajal interstitial cells or related stem cells, as stated above. For this reason, studying Kit (CD117) expression in tumor cells is the best immunostaining method for identifying GIST[14,18-20].

GISTs have malignant and insufficiently predictable biology and behavior, even with benign histological features. Morphologically, GISTs vary from spindle cell tumors to epithelioid and pleomorphic tumors. GISTs have approximately the same distribution in both sexes. Most are localized in the stomach (50%–60%) and the small intestine (30%). Esophageal, colorectal and rectal GISTs are rare (3%)[21].

The diagnosis of GIST is based on pathomorphological evidence by histological examination of biopsy material, and when taking a biopsy, the recommendations of NCCN. The NCCN organized a multidisciplinary panel composed of experts in surgery, pathology, medical oncology and molecular diagnostics to discuss the optimal approach for the care of patients with GIST at all stages of the disease [22,23].

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## SEARCH STRATEGY

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We performed a modified form of a narrative review where a search through scientific databases combined solid evidence from studies on vaccine effectiveness and safety in patients with gastrointestinal tumors and GISTs. The first literature search was carried out in Medline (PubMed) and Scopus bibliographic databases. Both MeSH and relevant free-text terms were used, as follows: (COVID-19 OR SARS-CoV-2) AND (GIST OR gastrointestinal stromal tumor) AND (vaccine\* OR mRNA). Our search was confined to articles published up to April 2022. Finally, references of retrieved publications were further hand-searched for supplements.

### **Official recommendations for COVID-19 vaccination in patients with GIST**

Up to date, no specific and official recommendations are included in the ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up for GIST (2022)[24]. However, ESMO statements on vaccination against COVID-19 in people with cancer conclude that all the approved COVID-19 vaccines could be administered to patients with cancer taking into account their effectiveness and safety, according to the official international recommendations[25]. Furthermore, ESMO has confirmed that the mass vaccination program is a crucial strategy for protecting against severe infection. This also stands for vulnerable patients, such as cancer patients, who take advantage of the most preferable benefit–risk ratio[25]. Since some patients with cancer, especially those with active malignancies, may experience a greater risk of severe SARS-CoV-2 infection, ESMO recommends COVID-19 vaccination. Despite reduced effectiveness for specific subgroups of cancer patients, the protection is still meaningful, and vaccination is strongly advised. Patients with hematological malignancies, particularly those undergoing cytotoxic chemotherapy, anti-CD20, CAR-T cell, or stem-cell-transplant-based treatments, are also among these populations.

### **Effectiveness and safety of COVID-19 vaccines in patients with GIST**

Prior to the COVID-19 pandemic, there was little evidence of the humoral and cellular immune responses to antiviral vaccination in cancer patients. Additionally, this primarily addressed the influenza vaccination[26,27]. Despite a general exclusion of cancer patients from the major clinical studies of COVID-19 and COVID-19 vaccination, subsequent results repeatedly proved the effectiveness

and safety of SARS-CoV-2 immunization in these patients. Overall, after complete COVID-19 immunization, persons with cancer have clinically significant seroconversion rates[28-32]. Although the efficiency of mRNA and adenoviral vector vaccines appears almost identical[30], there is a lack of comparative effectiveness data, particularly in cancer patients. Notably, when only one dose of an mRNA vaccine is delivered, the incidence of seroconversion is much reduced, emphasizing the necessity of vaccination completion and, eventually, booster for cancer patients[33,34].

However, there are not enough data from studies for COVID-19 vaccination in patients with GIST. There have been a few studies[30,35-39] that mainly recruited patients with gastrointestinal tumors, some with GIST, as summarized in Table 1. Thakkar *et al*[30] and Suenaga *et al*[35] demonstrated that even on chemotherapy, patients with gastrointestinal tumors tolerated COVID-19 vaccines well. Additionally, the effectiveness was assessed as adequate for SARS-CoV-2 infection protection. This observation was also valid for immunocompromised patients due to cancer treatment[36-38]. Given the scientific and logistical challenges in identifying cancer patients with weak or decreasing immunity, the global strategy of a booster dosage vaccination should be investigated for cancer patients. However, until better quality information on booster dosage benefits becomes available, international recommendations considering the risk of poor COVID-19 outcomes in cancer patients, vaccine availability/access, immunization progress, and the pandemic burden should be followed.

### ***Are there any risks for vaccination of patients with GIST/cancer***

The most significant driver for public health protection is the availability and equal access to COVID-19 immunization, with conformity to international criteria to be encouraged and supported. Therefore, vaccination plans have been established worldwide to prioritize vaccine delivery in various groups, including cancer patients. On the other hand, cancer patients do not constitute a homogenous group. And GISTs are among the rare cancer types.

In general, cancer patients can be divided into three groups: patients with active disease undergoing treatment, patients with chronic illness following specific therapy, and patients in the survival phase. Vaccination is essential to protect all of these patient groups[25]. If we translate this knowledge to the patients with GIST, we can assume that COVID-19 vaccination is strongly advised for them.

However, despite increasing compliance rates and existing evidence/data, 10%-20% of patients remain skeptical about the COVID-19 vaccine. These patients are at a higher risk of developing severe COVID-19 illness. In addition, they are a more likely source of SARS-CoV-2 transmission to other, more sensitive cancer patients[25]. It is critical to reinforce trust, education, and easy, transparent communication with those patients and their relatives based on the accumulated knowledge and better understanding of their concerns and hesitancy. In addition, communication of available data on vaccine safety and efficacy to people with cancer should also include assuring them that COVID-19 vaccines will not interfere with their cancer treatment[40]. Furthermore, there is no indication that COVID-19 immunizations substantially influence anticancer medication's efficacy or safety profile, such as cytotoxic chemotherapy, immune checkpoint inhibitors, or targeted therapies. Thus, COVID-19 vaccination is strongly advised[25]. More data on the preference for a specific type of vaccine and potential unusual interactions of SARS-CoV-2 vaccines with antineoplastic therapy should be collected by in-trial, post-trial, and registry monitoring.

Suppose an anticancer medication is urgently required for disease control. It is advised that suitable medication be implemented first, followed by COVID-19 immunization, as soon as the patient is clinically stable and significant symptoms are under control. To minimize misattribution of any short-term reactions/side effects, providers may consider administering anticancer medication and COVID-19 vaccinations on different days[41].

Therefore, since we do not have studies on the effectiveness and safety of COVID-19 vaccination for patients with GISTs, we have to rely on the official recommendations for patients with cancer generally. The data for rare diseases usually accumulate slowly. To protect patients from a "double jeopardy", informed consent and collaborative decision-making should be the rule when discussing the advantages and risks of COVID-19 immunization and SARS-CoV-2 infection.

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## **CONCLUSION**

Before the COVID-19 pandemic, most vaccination research with cancer patients was conducted for vaccines against hepatitis B, influenza and other infections. However, as the immune response is reduced in those patients, the risk of severe COVID-19 should be noted. Therefore, patients have to receive complete vaccination and booster doses to acquire higher levels of protection. This is also valid for patients with GIST. COVID-19 vaccination could be administered to patients who are even on therapy if some vaccine components are not contraindicated. The data show no significant difference in the efficacy of vaccines for the GIST/cancer population compared to other cancers. Oncologists have extensive experience in vaccinating cancer patients who are being treated, so they can effectively help save their patients' lives.

**Table 1 Studies of COVID-19 vaccination in patients with gastrointestinal tumors**

Ref.	Type of study	Type of COVID-19 vaccine	Participants	Efficacy/effectiveness	Adverse effects
Suenega <i>et al</i> [35], 2022	Retrospective observational study	mPNA (BNT162b2 or mRNA-1273)	Gastrointestinal cancer patients, <i>n</i> = 52	BNT162b2 (approximately 95%), mRNA-1273 (approximately 94%)	82.2% had adverse events: Injection site pain (approximately 67%), fatigue (approximately 12%), fever (approximately 6%), headache (approximately 4%), gastrointestinal problems (approximately 4%), redness (approximately 2%), insomnia (approximately 2%); no vaccine-related deaths
Fendler <i>et al</i> [36], 2022	Retrospective observational study	BNT162b2; mRNA-1273	115	mRNA vaccines (against omicron approximately 75%) (against delta approximately 79%); against omicron increased from 47.8% to 88.9% following a third vaccine dose	Injection site pain (approximately 63%), local swelling (9%), muscle pain (34%), fatigue (34%), headache (16%), fever (10%), chills (10%) and gastrointestinal events (10%); no vaccine-related deaths
Thakkar <i>et al</i> [30], 2021	Retrospective study	BNT162b2, mRNA-1273, Ad26.COV2.S	27 (14%) from 200 are with GIST	BNT162b2 (95%), mRNA-1273 (94%), Ad26.COV2.S (85%)	Sore arm (20%–37%), fatigue (5%–16%), muscle ache (5%–17%), fatigue (1%–5%), rash (1%–3%), redness (approximately 2%), other (1%–5%); no vaccine-related deaths
Embi <i>et al</i> [37], 2021	Observational study	BNT162b2; mRNA-1273	20 101 immunocompromised patients	BNT162b2 (71%), mRNA-1273 (81%)	Sore arm (20%–47%), fever (10%), fatigue (1%–5%), other (1%–5%); no vaccine-related deaths
Karacin <i>et al</i> [38], 2021	Prospective observational study	CoronaVac vaccine	47	Sero-response rate 63.8%	Pain at the injection site (4.2%), fever (2.1%), fatigue (4.2%–10.5%), headache (2.1%), and myalgia (2.1%), There were no serious side effects or toxic deaths
Ariamanesh <i>et al</i> [39], 2022	Prospective study	BBIBP-CorV	364 (32 patients with gastrointestinal tumors)	Sero-response rate 86.9%	Injection site pain, fever, fatigue, headache

## FOOTNOTES

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