Colorectal Cancer and COVID-19: Do We Need to Raise Awareness and Vigilance?

We read with great interest the article by Zhang et al1 regarding the higher risk of coronavirus disease 2019 (COVID-19) in patients with cancer compared with patients without a cancer diagnosis. In their study, gastrointestinal cancer (20 patients; 18.7%) ranked as the second most common cancer diagnosis among a total of 107 patients with cancer who were diagnosed with COVID-19,1 a finding that has been of concern among gastrointestinal surgeons and physicians. The question of why patients with gastrointestinal cancer are more vulnerable, and whether other routes of infection exist in addition to respiratory transmission, should arouse our interest.

The coronavirus spike protein helps the virus to enter the target cell through the angiotensin-converting enzyme 2 (ACE2) receptor. The transmembrane serine protease 2 (TMPRSS2) facilitates activation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein and increases the chance of the virus entering the target cell.2 The expression of ACE2 and TMPRSS2 in lung epithelium may increase the risk of SARS-CoV-2 infection and the severity of COVID-19.3 Clinical evidence has proven that SARS-CoV-2 uses ACE2 as a viral receptor for entry into the gastrointestinal system,4 and therefore higher levels of gene expression predict a greater chance of infection.

High levels of ACE2 and TMPRSS2 were found in the human gastrointestinal tract in addition to the respiratory tract.5 We used Gene Expression Profiling Interactive Analysis (GEPIA), a web-based tool that delivers fast and customized functions based on The Cancer Genome Atlas and Genotype-Tissue Expression (GTEx) Program data,6 to analyze the expression levels of ACE2 and TMPRSS2 proteins in normal intestinal tissues and colorectal cancer samples. It was found that the levels of ACE2 and TMPRSS2 expression in colorectal cancer tissues were statistically higher than those in normal tissues. There was no difference noted with regard to the levels of ACE2 and TMPRSS2 expression in colon and rectal cancer of different clinical stages, indicating that colorectal cancer of all clinical stages may be the undifferentiated target of SARS-CoV-2. Therefore, ACE2 and TMPRSS2 expression levels may be high in both tumor tissues and adjacent normal tissues in these patients. This distribution could further increase the possibility of SARS-CoV-2 invading and infecting patients with colorectal cancer.

A recent study of 73 hospitalized patients with COVID-19 demonstrated that the feces of approximately 53.42% of these patients was positive for SARS-CoV-2 RNA. Another analysis from He et al7 suggested that approximately 44% of the community transmission of COVID-19 could have occurred prior to symptom onset in infected patients. During colonoscopy or colorectal cancer surgery, physicians or surgeons may need to prevent aerosol contamination from the creation of laparoscopic pneumoperitoneum, or intestinal secretions and fecal contamination from the disposal of intestinal tract and tumors, even in asymptomatic patients. Therefore, gastrointestinal oncologists should raise awareness and vigilance regarding protection and actively take precautions to reduce the risk of infection from intestinal secretions and feces during and after examinations or surgeries in patients with colorectal cancer. Strict infection control measures should be enforced because gastrointestinal tumor surgery has a high risk of infection. Careful handling of intestinal tissue or tumor specimens should be practiced to reduce the risk of transmission caused by intestinal infection and to prevent nosocomial infections.

In addition, regardless of their clinical stage of disease, patients with colorectal cancer may be at high risk of contracting COVID-19 and are the crucial protection targets in epidemic prevention. Although further validation of clinical data is needed, these findings are of practical importance: patients with clinically mild or moderate COVID-19 with a diagnosis of colorectal cancer should be given special attention because of a possible longer course of disease or a higher risk of severe infection probability.

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We thank Niu et al for their interest in our article and their insightful comments regarding our results. The authors pointed out a key finding of our study, namely that patients with gastrointestinal cancers constituted a high percentage of the patients with cancer who were infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and these individuals were more likely to develop severe coronavirus disease 2019 (COVID-19) when infected. It is interesting to note that Niu et al suggested a number of mechanisms that may underpin the vulnerability of patients with gastrointestinal cancer to COVID-19 infection. Specifically, the authors examined the expression of 2 key proteins, namely the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane serine protease 2 (TMPRSS2), that mediate the entry of SARS-CoV-2 into human tissues. To this end, they analyzed gene expression data from the Gene Expression Profiling Interactive Analysis (GEPIA) database and found higher expression of both proteins in colorectal cancers compared with normal intestinal tissue. The authors thus rightfully raised their concerns regarding caring for patients with colorectal cancer during the ongoing COVID-19 pandemic. Here, we would like to investigate these points further relative to the published literature to date.

First, we agree with Niu et al that patients with gastrointestinal cancer constituted a substantial percentage of the patients with cancer in our cohort who were infected with SARS-CoV-2. Our data regarding 107 patients with cancer who were diagnosed with COVID-19 demonstrated that approximately 18.7% of patients were diagnosed with gastrointestinal cancer. This finding concurred with the other rates published by Wang et al (20.5%), Lee et al (19%), Yang et al (14%), Dai et al (12.4%), and Kuderer et al (12%) demonstrating that gastrointestinal cancer was one of the most common malignancies among patients with cancer who contracted COVID-19. However, to truly ascertain the susceptibility of patients with a specific type of cancer to COVID-19, the correct test would be to first determine the prevalence of COVID-19 among all patients with gastrointestinal cancer and then compare that prevalence across different cancer types. Thus, we would examine the assumption that patients with gastrointestinal cancer are particularly susceptible to COVID-19.

We next examined the mechanisms proposed by the authors. Niu et al proposed a number of concepts based on their preliminary evidence regarding gene expression of key virus entry–associated proteins. SARS-CoV-2 attaches to the target cell surface through the engagement of the viral spike (S) protein and the extracellular ACE2 receptor. Separately, TMPRSS2 cleaves and primes the S protein and drives the fusion of viral and cellular membranes. Similar to Niu et al, Bao et al and Wang et al also found that ACE2 and TMPRSS2 did demonstrate higher expression in patients with lung and gastrointestinal cancers compared with those with other malignancies. In addition, TMPRSS2 is regulated by testosterone and its metabolites, and therefore is suppressed by androgen deprivation therapy in patients with prostate cancer. It is interesting to note that early evidence has suggested that patients with prostate cancer who undergo androgen deprivation therapy may have a lower risk of SARS-CoV-2 infection. Collectively, these direct and indirect correlative findings support the plausible notion that the gastrointestinal tract represents a path for infection with SARS-CoV-2. On this note, SARS-CoV-2 RNA and coronavirus virions have been detected in surgically resected rectal specimens.

Third, emerging data have indicated that a dysfunctional gut microbiota also might play a role in the pathogenesis of COVID-19. Certain compositions of the gut microbiota were suggested to be either positively or negatively associated with levels of inflammatory cytokines, and were predictive of severe COVID-19, possibly through the modulation of fecal metabolites and host...