

SARS-CoV-2 pandemic: implications in the management of patients with colorectal cancer

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SUMMARY

The SARS-CoV-2 pandemic has already reached 3,207,248 patients with more than 225,000 deaths all over the world. Colorectal cancer is the third most diagnosed cancer worldwide, and the healthcare system is struggling to manage daily activities for elective cancer surgery. This review integrates clinical, microbiological, architectural and surgical aspects to develop indications on strategies to manage colorectal cancer patients and ensure safety during the pandemic. Telephone or virtual clinics must be encouraged and phone follow-up should be implemented. Indications for surgery must be rigorous, balancing the advantage of early surgical treatment and risks of treatment delay. To decrease the occupancy rate of intensive care unit beds, elective surgical treatment should be delayed until local endemic control, according to stage of disease. Patients with SARS-CoV-2 infection should be treated only after clinical recovery, two consecutive negative oropharyngeal swabs and, if available, a negative stool sample. Before any elective oncologic procedure, a multidisciplinary oncologic team including an anaesthesiologist and an infectious disease specialist must assess every patient to evaluate the risk of infection and its impact on perioperative morbidity, mortality and oncologic prognosis. The hospital should organise to manage all elective oncologic patients in an 'infection-free' area or refer them to a non-SARS-CoV-2 hospital.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-stranded RNA virus, is approximately 50-200 nm in diameter, and has four structural proteins known as S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins; the N protein holds the RNA genome, and the S, E, and M proteins together represent the viral envelope. The spike protein S is the protein responsible for allowing the virus to attach to and fuse with the membrane of a host cell through interaction with the membrane receptor ACE2, which has been proven to be a cell receptor for SARS-CoV-2.

SARS-CoV-2 is the etiologic agent of Coronavirus disease 2019 (COVID-19), which mainly affects the respiratory system. Due to tropism towards epithelial cells of other

systems such as the digestive tract, the disease may also be associated to systemic symptoms, such as diarrhoea.

The SARS-CoV-2 pandemic already reached 3,207,248 confirmed patients with more than 225,000 deaths all over the world (WHO, 2019). The disease has spread very rapidly in Italy, with 203,591 positive patients and 27,682 deaths (at 29th April 2020).

Cancer patients are more prone to infections due to the down-regulation of the immune system due to malnutrition, chemotherapy and surgery. Moreover, newer treatments with adverse effects on immune functions, such as various monoclonal antibodies, make cancer patients more susceptible to infections. Respiratory viruses severely affect individuals who are immunocompromised, and cancer patients receiving intensive chemotherapy and developing lymphocytopenia are at high risk for pneumonia, bacterial superinfection, persistent shedding, resistance to antiviral therapy and long-term decline of pulmonary function (Kamboj, 2009). In a recent study, Liang (2020) found that cancer patients treated by chemotherapy or surgery were more susceptible to SARS-CoV-2 infection and showed significantly higher clinical severity and poorer prognosis. According to a recent study, 20% of Italian patients who died from SARS-CoV-2 had an active cancer

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(Burki, 2020). Colorectal cancer (CRC) is the third most diagnosed cancer worldwide, with 1.8 million new cases and 861,000 deaths in 2018 (WHO, 2018), and presents as an emergency in 30% of cases (Barnett, 2013; Laine 2012). The bowel is one of the extra-pulmonary organs in which live viruses can be detected, and Chan *et al.* already found that infected patients developed intestinal symptoms after the 2003 SARS outbreak (Chan, 2004). Lei (2020) published the first retrospective paper on post-operative morbidity and mortality during the SARS-CoV-2 pandemic: 100% morbidity rate (post-operative pneumonia), 20.5% mortality, 15 of 34 patients required intensive care unit admission in the early post-operative period.

The healthcare system is struggling to treat an overwhelming number of critically ill patients and to manage daily activities, including cancer clinics and elective cancer surgery. There is a clear need to define multimodal, integrated and revised strategies to treat colorectal cancer patients, focusing on infection prevention and control (IPC) and making safety a priority for patients and healthcare professionals. Identifying a local opinion leader (surgeon champion) may be important to integrate the best clinical practice, implement changing behaviours, and improve IPC (Sartelli, 2020).

GENERAL RECOMMENDATIONS AND PREOPERATIVE SCREENING

Telephone or virtual clinics must be encouraged (British Society of Gastroenterology, 2020) and phone follow-up should be implemented (Cusack, 2010). A careful screening for possible SARS-CoV-2 infection is mandatory before admission. ACE2 is the main host cell receptor for SARS-CoV-2 and is not only highly expressed in the lung and oesophagus, but also in absorptive enterocytes of the ileum and colon (Zhang, 2020; Peiris, 2003). In fact, the ACE2 protein, which has been proven, by histologic and immunofluorescent staining, to be a cell receptor for SARS-CoV-2, is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelial, supporting the entry of the virus into the host cell (Xiao, 2020).

Detection of SARS-CoV-2 RNA in stools long after clinical recovery raises the possibility that patients could remain infectious after discharge (Cheng, 2004) and, if possible, presence of the virus should also be tested in stools with anal swab or stool RNA virus detection.

In more than 20% of SARS-CoV-2 positive patients the viral RNA detection by rRT-PCR (real-time reverse transcriptase-polymerase chain reaction) remained positive in faeces, even after molecular tests for RNA in the respiratory tract had become negative. This indicates that gastrointestinal infection and potential faecal-oral transmission may persist even after clearance in the respiratory tract.

Therefore, it would be advisable that transmission-based precautions for hospitalized patients with SARS-CoV-2 should continue if faeces results remain positive by rRT-PCR, especially if these patients will undergo laparoscopic procedures, thus avoiding a possible aerosolization of viral particles with the pneumoperitoneum technique or during open surgical procedures (Xiao, 2020).

Indications for surgery must be rigorous, considering IPC principles and balancing the advantage of an early surgical treatment (Grass, 2020) and the risks of treatment delay (Lee, 2019). To decrease workload and the occupancy rate of intensive care unit beds, elective surgical treatment

should be delayed until local endemic control, if possible for a maximum of 4 weeks, according to the stage of disease. Patients with SARS-CoV-2 infection should be treated only after clinical recovery, two consecutive negative oropharyngeal swabs and, if available, a negative stool sample. Before any elective oncologic procedure, a multidisciplinary oncologic team including an anaesthesiologist and an infectious disease specialist must assess every patient to evaluate the risk of infection and its impact on perioperative morbidity, mortality and oncologic prognosis. The hospital should organise to manage all elective oncologic patients in an 'infection-free' area or refer them to a non-SARS-CoV-2 hospital (Di Marzo, 2020a).

Studies made of the half-lives of SARS-CoV-2 and SARS-CoV-1 show that both are similar in aerosols, with median estimates of around 1.1 to 1.2 hours, and even the half-lives of the two viruses are similar on copper. The longest viability of both viruses was active in stainless steel and plastic; the estimated median of the half-life of SARS-CoV-2 was approximately 5.6 hours in stainless steel and 6.8 hours in plastic (van Doremalen, 2020).

These results indicate that aerosol transmission of SARS-CoV-2 can remain viable and infectious in aerosols and on surfaces for several hours. Therefore, these data are important for the prevention of nosocomial spread of the virus.

OPEN OR LAPAROSCOPIC APPROACH

During the pandemic, indications for laparoscopic or open approach in patients with CRC are still unclear. On the one hand, open surgical procedures would probably increase hospital stay, bed occupancy and likelihood of intensive care unit stay (Keller, 2016). On the other, laparoscopic surgery shortens hospital stay, but is questionable in critically ill patients with lung dysfunction, sepsis, or shock, and many authors have raised concerns about aerosolization of viral particles in the pneumoperitoneum (Choi, 2014). Perioperative actions to minimize the potential risk of diffusion of viral particles during surgery should include wearing enhanced personal protective equipment for operating room staff (two pairs of surgical gloves, coverall clothes with head cover, shoe covers, goggles, N95 respirator). Other precautions during laparoscopic surgery may include the use of lower intra-abdominal CO₂ pressure, a closed smoke suction system with ultralow particulate arrestance filter (ULPA), performing minimal incisions for trocars placement and evacuation of all smoke before specimen extraction.

SETTING UP AN OPERATING ROOM DURING THE SARS-COV-2 PANDEMIC

Ventilation system design plays a key role in mitigating the risks associated with airborne contamination, which is of particular relevance when considering the hospitalisation of SARS-CoV-2 patients. To mitigate the risk of cross contamination, all operating theatre suites should be ventilated via dedicated air handling units (Dept. Health/Estate and Facilities Div., 2007a), providing a minimum of 25 air changes per hour of outside fresh air into the operating theatre space in both conventional and ultra clean ventilation (UCV) systems (Dept. Health/Estate and Facilities Div., 2007b). This complete UCV system consists of recirculation fans and high efficiency particulate arrestance

(HEPA) filters within the canopy. SARS-CoV-2 range in size from 0.06 to 0.125 μm , falling squarely within the particle-size range that HEPA filters capture with extraordinary efficiency: 0.01 micron and above. It is incorrect to state that HEPA filters are unable to catch particles below 0.3 micron, like SARS-CoV-2 (Di Marzo, 2020b).

To eliminate the risk of exposing patients to airborne contaminants, operating theatre ventilation systems are generally designed to achieve a nominal air pressure (normally 25 Pascals) from within the theatre room with respect to adjacent rooms and corridors (Dept. Health/Estate and Facilities Div., 2007c). The operating room itself is provided with low-level extract. However, this is a small percentage of the overall air volume and is included to promote ventilation of the overall theatre room. As hospital theatre suites are generally designed to be positively pressurised, the larger proportion of air will always transfer to less sterile areas via door undercuts and pressure stabiliser dampers as would be defined in the pressure cascade design. With the scenario of treating both SARS-CoV-2 and Non SARS-CoV-2 patients within the same hospital, it is essential that modifications be defined with the existing systems to contain airflows within a defined number of rooms. Adjusting room pressure stabiliser dampers, re-balancing air volume in both supply and extract mode and the sealing of doors would need to be considered to mitigate the risk of air transfer to adjacent spaces, with different solutions potentially being adopted for the short, medium and long term.

The above adjustments to the ventilation regime in operating theatres would need to be accompanied by modification of clinical flows to achieve a separation of routes for SARS-CoV-2 and non-SARS-CoV-2 patients, as well as for personnel and SARS-CoV-2 patients. This segregation should ideally provide a separate emergency entrance and circulation into operating theatres and Intensive Care Units (ICU) for SARS-CoV-2 patients only. The reconfiguration strategy selected for each hospital may be influenced by its size, nature, configuration and location.

TREATMENT STRATEGIES IN PATIENTS WITH EARLY STAGE CRC

Surgical treatment of patients with Stage 0 (TisN0) CRC is postponed. It is important to schedule a periodic virtual follow-up, and patients should be instructed on which signs and symptoms have to be considered to contact the surgeon during the observation period. A multidisciplinary team must review the case within 4 weeks for patients with colon cancer and 2 weeks for patients with rectal cancer to evaluate progression of disease and arrange new consultation or endoscopy (Hu, 2020).

In patients with an endoscopically resected T1-N0 invasive cancer, the physician should review the pathology and meet the patient, preferably via virtual consultation. Observation and follow-up is indicated in a completely resected pedunculated or sessile polyp with favourable histologic features (grade 1 or 2, no angiolymphatic invasion, and negative resection margin) (Markowitz, 1997; Alimonti 2008; Yoshii, 2014). In case of fragmented specimen, without margins assessment or with unfavourable histopathology (grade 3 or 4, angiolymphatic invasion, positive resection margin, high grade tumour-budding) (Bosch, 2013; Mou, 2013), an additional workup should be done to indicate radical surgery (Belderbos, 2014). If the

tumour is below 8 cm from the anal verge and less than 3 cm in diameter, transanal resection may be considered, including advanced techniques (Clancy, 2015; Nash, 2009). During the observation period, patients with low rectal cancers should be examined within 2 weeks by digital rectal examination, and tumour markers checked as a baseline benchmark (Mulcahy, 1999; Zhai, 2018). For patients strongly motivated to surgery the best choice remains to be defined, and this option can be considered after an adequate informed consent about the risks.

In patients with T2N0 cancers, radical surgery is the preferred treatment and should be postponed. Screening and follow-up for SARS-CoV-2 must be arranged as previously indicated.

TREATMENT STRATEGIES FOR PATIENTS WITH ADVANCED CRC

In patients with colon T3-4 N0-2 and clinical T4b or bulky nodal disease, neoadjuvant chemotherapy should be evaluated on a case-by-case basis, and radical surgery postponed. Timing of surgery should be determined after clinical re-evaluation performed after 2 to 3 cycles (Liu, 2016; de Gooyer, 2019).

In patients with T3N0 rectal cancer below 12 cm from the anal verge, to decrease the patient's exposures and risk of infection, a short-course radiation therapy is the recommended option.

In T3-4 and/or N+ rectal cancers below 12 cm from the anal margin, to reduce hospital exposure, total neoadjuvant therapy (TNT) should be strongly recommended, considering a short course radiation regimen. Patients strongly motivated for surgery should be informed that neoadjuvant chemo-radiotherapy could achieve higher tumour shrinkage, facilitate surgical resection, and reduce the probability of local recurrence. It is generally recommended to perform surgery 8 to 12 weeks after neoadjuvant therapy preceded by MRI at week 6-8 (Beets-Tan, 2018). This limit can be prolonged in case of a longer pandemic, as many studies reported a higher rate of complete pathological responses in patients with the longest delay (Habr-Gama 2009; Garcia-Aguilar, 2015). Patients with a clinically complete response must be re-evaluated within 4 weeks. Although the watch-and-wait strategy is still controversial, some studies show that the overall survival rate is similar to that of operated patients (Renehan, 2016). Patients strongly motivated for surgery could be advised to conduct a short-term observation and clinical re-evaluation within two weeks with a digital rectal examination, endoscopy, and tumour markers (Mulcahy, 1999). After the epidemic is over or within 4 weeks, the patients should be considered for radical treatment.

TREATMENT STRATEGIES IN PATIENTS WITH CRC PRESENTING IN EMERGENCY

For patients presenting in an acute setting, the first option should be the treatment of the acute clinical condition, considering surgery, interventional radiology or endoscopy. In negative SARS-CoV-2 patients with obstructive colorectal cancer and good performance status, radical surgical treatment should be the procedure of choice (Pisano, 2018). In patients unfit for surgery, stenting may be a valid option except in patients with low rectal obstruction, in whom a diverting colostomy should be performed

(Shimura, 2016). A correlation between bevacizumab and stent-related perforation has been reported (Cennamo, 2009), and the European Society of Gastrointestinal Endoscopy (ESGE) clinical guidelines do not recommend stenting patients already treated or planned to be treated with antiangiogenic drugs (van Hooft, 2020). After successful stenting, neoadjuvant treatment should be considered as a bridge to definitive radical surgery.

In SARS-CoV-2 positive patients presenting with obstructive cancer, endoscopic stenting, if available and feasible, should be considered as the first option (Young, 2015) with a diverting stoma as a valid alternative. A resection and diverting stoma should be performed in patients presenting with a perforated cancer at the tumour site. If the perforation is proximal to the tumour, simultaneous tumour resection and management of proximal perforation is indicated (Pisano, 2018). In bleeding cancers, angiography, interventional radiology (Park, 2020) and endoscopic local treatment should be considered as an alternative to surgery.

CONCLUSIONS

This review integrates clinical, microbiological, architectural and surgical aspects to develop indications on strategies to manage colorectal cancer patients during the SARS-CoV-2 pandemic.

Elective surgical treatment should be delayed until local endemic control and according to stage of disease. Indications for surgery must be rigorous, balancing the advantage of early surgical treatment and risks of treatment delay. Patients with SARS-CoV-2 infection should be treated only after clinical recovery, two consecutive negative oropharyngeal swabs and, if available, a negative stool sample. Before any elective oncologic procedure, a multidisciplinary oncologic team including an anaesthesiologist and an infectious disease specialist must assess every patient to evaluate the risk of infection and its impact on perioperative morbidity, mortality and oncologic prognosis. Regional and national governments should provide clear leadership and strong economic support to manage colorectal cancer patients and ensure safety during the SARS-CoV-2 pandemic.

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