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Lower Gastrointestinal Cancers (AB Benson, Section Editor)

Lessons Learned in Managing Patients with Colorectal Cancer During the COVID-19 Pandemic

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Opinion statement

The COVID-19 pandemic forced us to rapidly and dramatically shift our medical priorities and decision making. With little literature or experience to rely on, the initial priority was to minimize patient exposure to the hospital and to others. It remains unclear whether cancer patients are at higher risk of infection or serious complications, or if it is our traditional therapies that place them to be at higher risk. By far, the greatest negative impact was on screening. Routine colonoscopies were considered elective, and as a result, delays in diagnosis will be felt for years to come. The most positive changes were the incorporation of tele-visits, increased use of oral therapies, alterations in treatment schedules of both chemotherapy and radiation, and an increased emphasis on neoadjuvant therapy. These too will be felt for years to come. The colorectal cancer medical community has responded collaboratively and effectively to maintain treatment and to optimize outcomes for our patients during the COVID-19 pandemic.

Introduction

The pandemic of coronavirus disease 2019 (COVID-19), a disease caused by the novel human coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), led to signification changes in healthcare infrastructure and challenges in cancer care starting in late 2019. COVID-19-infected patients can present

asymptomatically to critically ill, and the infection is associated with high intubation rates and in-hospital mortality [1, 2]. The dominant route of transmission is respiratory with reports of variable infectivity rates ranging from 17 to 62% and an estimated one-half of cases transmitted from asymptomatic individuals [3–8]. As the first wave of COVID-19 cases overwhelmed medical systems across the world, many hospitals scrambled to redistribute medical providers to care for COVID-19 patients, stopped non-emergency surgical procedures, functioned at reduced capacity, and adopted new systems to limit patient gatherings and exposures.

In the USA, colorectal cancer (CRC) is the third most commonly diagnosed cancer in men and women with an estimated 147,950 new cases diagnosed in 2020 [9]. While the majority of newly diagnosed CRCs is locoregional and associated 5-year survival rates of 71–90%, about 22% of new cases are metastatic at diagnosis and associated with significant mortality (5-year survival rate of 14.3%). Unfortunately, the pandemic led to marked reductions in elective colonoscopies, a screening modality known to significantly reduce CRC-related mortality [10]. The pandemic also forced cancer patients and medical providers to urgently balance the risks of potential COVID-19 exposures, morbidity, and mortality with the non-elective treatments for cancers.

As of April 4, 2021, the cumulative global COVID-19 cases exceeded 130 million with over two million attributable deaths since the beginning of the pandemic [11]. Over four million new cases are still diagnosed weekly. While the pandemic landscape is evolving with novel treatments and most recently vaccination distribution, we must continue to advocate for our cancer patients and balance the risks and benefits of CRC interventions. Here, we review what we have learned so far in managing CRC patients based on published studies and reflect upon our personal experiences during these unprecedented pandemic times.

COVID-19 and risks in cancer patients

The immunosuppressive nature of cancer, myelosuppressive therapies, older demographic, and frequent medical facility exposures raise concerns for COVID-19 infections in the cancer population. A few large studies suggest that cancer patients have higher risks of complications and death from COVID-19 infection. In May 2020, the COVID-19 and Cancer Consortium (CCC-19) published results from a retrospective cohort study of 928 USA and UK patients diagnosed with COVID-19 across many cancer subtypes [12]. The mortality rate within 30 days of COVID-19 diagnoses was 13%, and 26% of patients met a secondary composite endpoint of severe illness including death, hospital or ICU admission, mechanical ventilation, or a combination of these. Post-hoc analyses revealed that older age, race, number of co-morbidities, hematologic malignancy, Eastern Cooperative Oncology Group performance status of two or higher, treatment with azithromycin and/or hydroxychloroquine, and progressive or unknown cancer status were associated with increased rates of secondary composite endpoints. The UK Coronavirus Cancer Monitoring Project's (UKCCMP) prospective observational study of 800 UK cancer patients reported a 28% mortality rate with age and comorbidities (hypertension and cardiovascular disease) being significantly associated with mortality [13]. A systematic review and pooled analysis of over 18,650 cancer patients with COVID-19 from 52 international studies reported a 25.6% mortality rate [14•]. Other individual and pooled studies report mortality rates between 12 and 30% and suggest that a cancer diagnosis is associated with worse COVID-19 outcomes [15–21]. In contrast, some studies report more comparable outcomes between cancer and non-cancer patients [22, 23].

The effect of cancer therapy on COVID-19 outcomes is still being described. In patients with solid tumors in the CCC-19 study, subgroup analyses did not suggest associations between active cytotoxic therapy, non-cytotoxic therapy, or recent surgery and clinical outcomes although these were descriptive results with no statistical analyses. In the UKCCMP study, after adjusting for age, gender, and comorbidities, cancer-related therapy (chemotherapy, immunotherapy, targeted therapy, hormonal therapy, and radiotherapy) in the 4 weeks prior to COVID-19 diagnosis had no significant effect on mortality [13]. A study of 585 patients in New York City, USA, reported similar outcomes in cancer versus non-cancer patients, and 45% of the cancer patients had received immunosuppressive therapy within 90 days of hospital admission [23]. Other centers have also reported low rates of COVID-19 infection while on systemic therapy [24]. In contrast, some studies suggest that mortality is higher in patients having received active cancer treatment [17, 25, 26]. A large case-control study including over 73 million electronic medical records reported patients with cancer had significantly higher risks of COVID-19 infection and worse outcomes [21]. Conflicting results in mortality may be due to variations in the underlying characteristics of cancer patients across studies. While the identification of factors and patient subgroups continue to evolve, the US Center for Disease Control (CDC) has included cancer as a condition portending high risks of severe COVID-19 illness, and in clinical practice, these patients require special considerations in aggressiveness of cancer management while mitigating their infectious risks [27].

It is important to recognize cancer patients comprise a heterogenous group with different ages, comorbidities, risk factors, treatment strategies, stages of progression, and prognoses. Few studies suggest that hematologic and lung cancer subtypes are associated with higher COVID-19 risks [12, 20, 26, 28]. There are limited data specifically related to CRC and COVID-19. Lee et al. studied COVID-19 risks across multiple cancers and also reported that patients with leukemia had statistically significant increased COVID-19-related fatality, but such findings were not found in CRC patients where the case-fatality rate was 0.282 (OR 0.85, 95% CI 0.44–1.64, p = 0.63) [29]. Tuechh et al. reported no increased COVID-19-related mortality in CRC patients having recently undergone surgical resection [30]. Further studies with larger populations of CRC patients are required to better characterize the outcomes of COVID-19 patients in this group.

Screening and impact on early-stage colorectal cancer

Starting March 2020, many healthcare systems mandated delaying non-emergent screening and diagnostic endoscopies due to personal protective equipment (PPE), operating room, and staff constraints. In addition, endoscopies are aerosolizing procedures conferring high COVID-19 transmission risk [31]. However, colonoscopies are also crucial in early CRC prevention and considerably reduce CRC incidence and mortality by over 60% in populations through removal of precancerous adenomas [10, 32].

A study across four population-based National Health Service (NHS) datasets in England revealed a 63% relative reduction in colonoscopy referrals and 92% relative reduction in number of colonoscopies performed after the

first lockdown in April 2020 compared to 2019 levels [33]. Another UK study reported colonoscopy activity dropped to a nadir of 5% relative to pre-COVID-19 activity and was associated with a 58% reduction in weekly cancer diagnoses [34]. In March 2020, the US Surgeon General and US Centers for Medicare and Medicaid Service issued guidance to delay non-urgent procedures. Consequently, a USA study similarly noted a reduction of about 50% in newly identified CRC cases towards the end of March and into April 2020 compared to pre-COVID-19 times [35]. The Veterans Affairs Health System, one of the largest integrated health systems in the USA, reported a striking 78% decrease in upper endoscopies and 93% decrease in colonoscopies performed in April 2020 compared with pre-COVID historical controls [36••].

Mandated colonoscopy cancelations and delays raise concerns about missing early CRC diagnoses in populations. Estimation models suggest delays in colonoscopy screening up to 12 months after a positive fecal immunochemical test (FIT) result in loss of screening benefit, and early prediction models in response to COVID-19 suggest a 6-month delay would result in stage I to II progression in 3% of patients [37, 38]. Other prediction models estimate an excess of over 4000 CRC deaths over the next 10 years due to the pandemic impacts on screening [39]. The University of Pennsylvania, USA, already reported a 45% decrease in new gastrointestinal (GI) malignancy visits with the highest decrease of 53% in new CRC cases likely attributed to the 91% drop in colonoscopies performed during the pandemic [40].

Alternative methods such as non-invasive, at-home FIT testing and implementation of outreach programs were recommended in place of invasive colonoscopies for screening and to prioritize patients for colonoscopies [41]. However, the increase in non-invasive screening measures did not compensate for the overall decrease in all screening modalities at some institutions [42]. The actual clinical repercussions of alternative screenings, outreach programs, and delayed colonoscopy screenings especially in underserved populations may not be known for some time. Continued optimization of peri-procedural safety and screening methods is crucial for early CRC diagnosis and reducing mortality.

The anticipated pandemic effects across socioeconomic and geographic groups that historically experienced disparities in CRC outcomes are especially concerning. African Americans, especially men, carry the highest incidence and mortality rate of CRC across all major racial subgroups in the USA followed by American Indian and Alaska Natives [43]. Disparities may be partly attributed to disproportionally lower socioeconomic status, comorbidities, prevalence of CRC risk factors, rates of screening, and access to healthcare [44]. Historically, marginalized racial and socioeconomic groups also have lower rates of CRC screening attributed to structural barriers like limited access to healthcare, lack of insurance, and reported lower rates of provider recommendations [44–47]. Unfortunately, in the USA, these groups among other marginalized populations also experienced higher rates of financial instability, unemployment, COVID-19 infection, and mortality during the pandemic [48]. Many experts are proposing strategies to address the resulting challenges in screening and CRC care in underserved communities such as mailing at-home FIT tests, ensuring community health centers have support and access to colonoscopies, and increasing research in these groups [49, 50]. Community-based studies are imperative to understand healthcare limitations and develop better strategies to serve these at-

risk populations moving forward who have likely suffered the most from the pandemic.

We must also consider the pandemic effects in another unfortunate and increasingly prevalent group, young-onset CRC patients. In the past 3 decades, there has been a disturbing global rise in CRCs in individuals under 50 years of age [44]. These CRCs are more likely to be anatomically distal primaries and disproportionately diagnosed at advanced stages compared to CRCs in older patients. While the etiology of this trend has yet to be fully elucidated, in 2018, the American Cancer Society updated their recommendations to start average-risk CRC screening at age 45 which was supported by the US Preventive Services Task Force in May 2021 [51, 52]. While we wait for studies to confirm this, there are concerns that delays in screening and seeking medical attention for early GI symptoms during the pandemic will result in more advanced diagnoses in young patients in the upcoming months to years. In the interim, it is important for providers to recognize concerning symptoms and promptly initiate evaluation as our medical systems emerge from pandemic constraints.

Navigating institutional changes

Many oncology departments found themselves restructuring, re-locating oncologists to care for COVID-19 patients, and frequently communicating updates at the height of the pandemic. One organization, New York Presbyterian Hospital systems, reported their experience in cancer leadership and resource management during the height of the pandemic in New York City, USA, a city that experienced exceptionally high rates of infection and resource constraints [53]. At Lombardi Comprehensive Cancer Center, we implemented department-wide weekly meetings to discuss COVID-19 updates, safety concerns, and patient care. Similar to other institutions, we employed a system where we called patients prior to their appointments to screen for COVID-19 symptoms and redirected them to COVID-19 testing, the emergency department, a rescheduled in-person visit after a negative COVID-19 test, or a tele-visit if they screened positive. The entire department was briefed on pathways to follow when encountering patients displaying symptoms of COVID-19. Frequent weekly debriefings helped us share our experiences and brainstorm ways to improve our approach to clinical care and personal safety in unprecedented times.

Clinic visits and digital health

Most institutions, including ours, transitioned to primarily using tele-visits and significantly limiting in-person clinic appointments to minimize exposures at the height of the pandemic. Early surveys published by other institutions demonstrate variable levels of patient anxiety and overall favorable feedback on utilizing tele-visits [54–56]. In our experience, the majority of patients appreciated the convenience of a remote physician visit and felt their questions were appropriately addressed. Others conveyed tele-visits lacked the "human-touch" they desired from their treating teams and preferred an in-person experience. End-of-life and goals-of-care discussions can be especially emotionally challenging for patients and physicians through digital systems that

minimize non-verbal communication.

Initially, our teams had to troubleshoot technical challenges such as connectivity issues, inaudibility, or poor video quality. Some patients did not have camera devices, and others were uncomfortable managing the technology. With streamlined COVID-19 testing, vaccination, and a trend towards normalization of hospital procedures, we are seeing more patients back in the clinic over the past few months. We have started offering stable patients the option for tele-visit, which are now significantly improved in quality, versus a clinic visit or alternating visit types when deemed appropriate. Most patients seem to favor this approach. We anticipate continuing tele-health visits for appropriate patients who are comfortable with this modality even after resolution of the pandemic.

Systemic therapy

Multiple expert oncology groups released recommendations for modifying standard-of-care (SOC) treatments to balance the benefits of systemic therapies against the risks of patient and healthcare personnel exposures to COVID-19 [57, 58, 59••, 60••] (Table 1). While all potential CRC scenarios and recommendations will not be reviewed here, the overarching themes were to reduce risks of COVID-19 infection by minimizing healthcare exposures, myelosuppression, and treatments with minimal benefit while still adequately controlling disease in the palliative setting and aggressively treating in the curative setting.

Proposed SOC treatment alterations included utilizing equivalent oral over intravenous drugs when feasible (such as choosing capecitabine in place of 5-fluorouracil [5-FU]), alternative capecitabine scheduling to minimize toxicity, avoiding regimens with significant grade 3 or 4 toxicities, considering dose reductions proactively, and adding growth factors to minimize neutropenia [64–66]. Regimens like FOLFOXIRI and TAS-102, associated with 50% and 38% rates of grade 3/4 neutropenia, respectively, should be carefully considered or started with dose reductions to prevent excessive myelosuppression and hospitalizations [67, 68]. Longer immunotherapy dosing intervals with similar pharmacokinetics were favored to reduce infusion visits [69, 70]. When using 5-FU, experts recommended dropping the bolus which is associated with higher rates of hematologic toxicity and unclear survival benefit [71].

For oxaliplatin-based regimens in the metastatic setting, treatment breaks, intermittent oxaliplatin dosing, or de-escalating to pyrimidine analogue maintenance (favoring oral drugs) after 6 to 8 cycles of induction therapy are established treatment strategies that could especially be considered during the pandemic to minimize toxicities and healthcare visits [72–74]. In the stage II CRC, the marginal and controversial survival benefit with adjuvant fluoropyrimidine and no proven survival benefit with addition of oxaliplatin should be weighed against the risks of COVID-19 infectivity when considering treatment versus observation [75, 76]. In stage III CRC where adjuvant chemotherapy has clear survival benefit, limiting treatment to 3 rather than 6 months based on the IDEA collaboration trial and thereby limiting toxicities and infection exposures without significantly sacrificing survival benefit should also be considered [77••]. Globally, groups have started to publish their experiences

Table 1. General expert group recommendations in lower gastrointestinal cancers during COVID-19

Expert group [Reference]	General	Adjuvant setting	Metastatic	Surgery and radiation
COVID-19 Working Group of the NCCN Colon, Rectal, and Anal Cancers Guidelines [57••]	• Minimize in-person interactions to essential contacts • Minimize blood tests, scans, prescriptions, routine tests • Use telephone and telemedicine visits in place of routine in-person visits • Delay surveillance colonoscopies • Extend visits for central venous access catheter flushes to at least 12 weeks • Consider delaying non-critical biopsies • Consider postponing enrollment to clinical trials that require multiple biopsies and frequent healthcare-setting exposures	• In stage III CRC, consider 3 months over 6 months based on IDEA trial • Weigh additional benefit of 6 months in high-risk stage III CRC patients against risk of frequent in-person encounters • If FOLFOX required, consider omitting bolus	• Consider single-agent capecitabine when reasonable or CAPOX on a 21-day cycle over 14-day cycle regimens • Limit FOLFOXIRI use to extenuating circumstances only given toxicities • Oral therapies favored when appropriate • When single agent capecitabine indicated, consider omitting routine labs in absence of symptoms • Consider alternative capecitabine dosing to minimize toxicity and monitoring (every other week dosing rather than 14-day dosing) • Consider longer treatment intervals (nivolumab IV 480 mg q8 weeks or pembrolizumab 400 mg IV q6 weeks) • Consider empiric dose reductions in patients with comorbidities • Consider dose reductions over pegfilgrastim administration unless an at-home, self-administration option exists • Consider upfront IO therapy instead of chemotherapy in MSI-H CRC	• Endorses surgical recommendations from Society of Surgical Oncologists for Colorectal Cancer • If stages II and III and unable to have surgery due to COVID-19 constraints, consider course of neoadjuvant capecitabine or CAPOX as bridge to surgery • Consider SCRT (5 fractions instead of 28) • Consider delaying rectal cancer resection after SCRT by 6–8 weeks or longer to prevent surgery during COVID-19 surges • Consider postponing local or locoregional therapies until COVID-19 risk diminishes

Table 1. (Continued)

Expert group [Reference]	General	Adjuvant setting	Metastatic	Surgery and radiation
			• For maintenance, consider capecitabine without biologic • Check CEA at times scans would be considered where stable labs may suffice for clinical decision-making • In 5-FU/capecitabine refractory cases, consider targeted therapy when feasible • Prioritize every-other-week cetuximab over weekly dosing • Discuss goals of care including intubation and resuscitation status	
US Colorectal Cancer Alliance [58••]	• Avoid clinic and hospital exposure when possible • Maintain optimal clinical outcomes, especially in curative setting • Favor adding prophylactic growth factor support in patients with borderline neutrophil counts at baseline with caution as its use in active COVID-19 infection increases risk of capillary leak syndrome • Manage oral therapy with telemedicine visits and outside labs • Extend visits for central venous access catheter flushes to 6–8 weeks	• Consider bespoke ctDNA testing for adjuvant decision making • In stage III CRC, start adjuvant chemotherapy 4–8-week post-op; do not delay chemotherapy due to inferior survival outcomes • Consider switching IV 5-FU to oral capecitabine	• Skip cycles of treatment (e.g., bevacizumab or IO therapy with long half-lives) • Reduce myelosuppression • Avoid grade 3–4 toxicity requiring emergency room visits/hospitalization • If on intensive regimen, consider dose modifications by as much as 25% proactively particularly in first few cycles to ensure grade 3–4 toxicities do not emerge • Drop bolus 5-FU • Change IV 5-FU to oral capecitabine • Consider capecitabine 1000–1500 mg BID Monday-Friday or a 7-day on, 7-day off regimen • Avoid full dose capecitabine alone or with chemotherapy	• Delay surgeries when appropriate (may be upwards of 2–3 months) • Primary resections, obstruction, severe bleeding treatment should continue if feasible • Elective liver or other metastatic resections should not commence without justification; consider maintenance oral chemotherapy or treatment holiday as a bridge until surgery is safe to do • Consider delaying rectal resections after major neo-adjuvant response in select cases • Consider SCRT when possible

Table 1. (Continued)

Expert group [Reference]	General	Adjuvant setting	Metastatic	Surgery and radiation
			as it is associated with more mucositis and diarrhea	
City of Hope National Medical Center [59]		• Stage II/III rectal cancer should receive standard neoadjuvant/TNT with SCRT if surgery is feasible and institutional resources are strained • When operating capacity is diminished, consider neoadjuvant FOLFOX/CAPOX in stage II CRC to delay surgery	• Careful treatment planning required for metastatic CRC patients planning curative resection • Consider continuing chemotherapy to delay surgery but being mindful of short window of opportunity and risk of disease progression	• Life-threatening complications related to primary tumor or metastases warrant surgical treatment unless patient is terminal with no further treatment options • Oncological urgent cases but not emergency cases (stages I, II, III colon cancer, stage I rectal, stage II/III rectal after chemoradiation, stage IV cancer with POD on chemotherapy) can be delayed • Surgery delays beyond 6–8 weeks should be avoided in stages I–III CRC due to inferior OS
Expert Oncologist Group [60••]	• Eliminate treatments with marginal benefit • Reduce time patients spend in health care facility by using telehealth • Prophylactic growth factors may be warranted but ideally through take-home versions to minimize clinic visits • Consider reducing frequency of safety labs in stable patients on long-term therapy • Postpone routine surveillance visits	• Consider delaying or foregoing adjuvant chemo in high-risk stage II CRC • Consider delaying/forgoing adjuvant chemo in stage II vs. shortening duration (3 vs. 6 months) and/or using capecitabine in place of IV 5-FU in regimens • In adjuvant stage II (high-risk) or stage III: prefer CAPOX over FOLFOX, consider stopping therapy at 3 months or switching to capecitabine or 5-FU alone for remainder	• Discuss risks vs. benefits of treatment compared with risk of acquiring and suffering morbidity related to COVID-19 • If maintenance therapy desired, consider capecitabine monotherapy +/- bevacizumab • If disease is 5-FU refractory, irinotecan with or without biologics would be preferred over FOLFIRI • Consider regorafenib over TAS-102 due to risk of	• Use pre-operative SCRT in localized rectal cancer and surgery at 12 weeks • High-risk localized rectal cancer: proceed with neoadjuvant chemotherapy with a preference for CAPOX over FOLFOX followed by SBRT • T4 or N2 rectal cancer with major response to chemoradiation: discuss surgical resection and consider wait-and-watch strategy with frequent follow-up surveillance

Table 1. (Continued)

Expert group [Reference]	General	Adjuvant setting	Metastatic	Surgery and radiation
	• Delay restaging scans in metastatic patients who are stable • Obtain labs closer to home, consider in-home collection	• Consider early discontinuation of oxaliplatin • For low-risk CRC, discuss myelosuppression of oxaliplatin and use of capecitabine monotherapy	leukopenia and neutropenia for later-line therapy • Consider less frequent evaluation of patients on regorafenib • Consider alternative-week dosing of TAS-102 (7 days on/7 days off) • Consider break from therapy if otherwise stable • Double time between infusions when on IO therapy • Delay interval between treatments • For IO therapy durations > 12 months, consider holding IO therapy • Favor regimens that can be self-administered at home (oral, subcutaneous, intramuscular over IV) • Discontinue 5-FU bolus • Consider avoiding FOLFIRINOX (> 50% neutropenia rate) in favor of modified dosing and/or number of combination drugs • Consider dose reductions to avoid neutropenia	• Delay surgical intervention in localized rectal cancer after neoadjuvant therapy up to 12 weeks on observation • Localized CRC < T4: surgery within normal timeframe if possible • Particular cases CRC T4: proceed with or delay surgical resection, some suggest consideration of neoadjuvant chemotherapy (preference for CAPOX) and surgery after COVID-19 pandemic • Patients at high risk for COVID-19 complications: delay surgery between 4 and 6 weeks according to benefit-risk ratio • Favor hypo fractionated regimens vs. conventional fractionated
ESMO [61]	• High-priority outpatient visit patients include unstable patients or symptomatic newly diagnosed cancer patients • Low-priority outpatient visits include second opinions, follow-up out of study,	• Adjuvant treatment for high-risk stage II CRC, molecular profiling and dihydropyrimidine dehydrogenase testing to help treatment decision in stage II CRC, and adjuvant treatment in low- and	• First-line metastatic treatment in patients with ECOG PS 0-2 is medium priority • Treatments with modest benefit, first-line therapy in patients with ECOG PS 3, and treatment for symptomatic	• High-priority surgeries include obstruction, perforation, gastrointestinal bleed, post-surgical complication, bone fracture with spinal cord compression

Table 1. (Continued)

Expert group [Reference]	General	Adjuvant setting	Metastatic	Surgery and radiation
	restaging in metastatic non-curative setting, follow up on maintenance treatment • High priority for radiological/endoscopic evaluation include obstruction, bleeding, perforation, post-surgical complication, and bone fractures due to metastases • Low priority for radiological/endoscopic evaluation includes secondary CRC prevention, restaging in third/fourth-line treatment, restaging in metastatic non-curative setting • Perform blood tests near home	high-risk CRC are medium priority • Consider CAPOX over FOLFOX and administration of 3 over 6 months adjuvant therapy in stage III CRC • Neoadjuvant/adjuvant therapy in stage II/III rectal cancer treatment is medium priority	slowly growing recurrent disease are low priority • Consider 2-week administration of cetuximab rather than weekly • Use granulocyte growth factors for patients at risk of neutropenia • For poor molecular prognosis patients, continue treatment in frame of clinical trials	• Low-priority surgeries include early-stage rectal cancer after complete radiographic response after radiotherapy, prophylactic surgery, or biopsy of metastatic lesions in advanced, late-line treated patients for molecular profiling • Radiation to severe complications from cancer (organ failure from compression, bleeding, pain, fractures, mediastinal masses with compression, symptomatic brain metastases) are high priority • Radiation for neoadjuvant/adjuvant stage II/III rectal cancer and oligometastatic disease where systemic therapy is contraindicated is medium priority • Delay radiation for slow-growing tumors and where treatment benefits are modest
University of Chicago Department of Surgery [62]				• If operating room or resource constraints present, consider local excision rather than TME for stage I rectal cancers • High-risk stage I rectal cancer should undergo TME when safe from COVID-19 perspective

Table 1. (Continued)

Expert group [Reference]	General	Adjuvant setting	Metastatic	Surgery and radiation
				• If delays to OR, consider chemoradiotherapy for stage I rectal cancer • SCRT recommended over LCRT for stage II/III rectal cancers • Consider delaying surgery up to 8 weeks after SCRT or LCRT but not longer • Consider TNT for locally advanced rectal cancer • Consider "watch and wait" approach for patients with complete clinical response after TNT in rectal cancer • Address urgent cancer complications with surgery as appropriate • Consider stenting or simple diversion for obstruction
International Expert Consensus Statement Regarding Radiotherapy [63]				• TME without preoperative radiotherapy recommended for early-stage rectal cancers • Consider TME alone (with consideration of SCRT in countries where high quality surgery cannot be assured) for intermediate stage rectal cancers • Consider SCRT with delay to surgery in locally advanced rectal cancers • TNT recommended for advanced rectal cancer

CRC colorectal cancer, *ctDNA* circulating tumor DNA, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *ESMO* European Society of Medical Oncology, *5-FU* 5-fluorouracil, *IO* immune oncology, *LCRT* long-course radiation therapy, *MSI-H* microsatellite-high, *OR* operating room, *OS* overall survival, *POD* progression of disease, *SCRT* short-course radiation therapy, *TME* total mesorectal excision, *TNT* total neoadjuvant therapy

with treatment delays or modifications in CRC patients during the pandemic [78–80]. However, consequent survival outcomes will require long-term follow-up.

Radiation therapy

Radiation therapy is incorporated in SOC treatment for locally advanced, early-stage rectal cancer. It plays a more limited role in colon cancer for locoregional control and occasionally for oligometastatic disease with curative intent. During the pandemic, expert groups made recommendations for prioritization of radiation treatment based on optimization of locoregional control and survival benefit which were supported by the American Society of Radiation Oncology [61, 63] (Table 1). Severe complications such as cord compression, brain metastases, uncontrolled bleeding, fractures, and severe pain among others were prioritized, and neoadjuvant radiation regimens for advanced rectal cancer with curative potential were also recommended to continue without delay. In general, locoregional therapy for patients with metastatic cancer with limited survival benefit or for patients with slow-growing tumors was considered lower priority.

The general consensus has been to treat patients with SOC regimens modified to reduce COVID-19 exposures but without compromising survival outcomes. For instance, in early-stage rectal cancer, primarily T3 or T4 disease or any T with nodal disease, SOC treatment regimens include either short-course radiotherapy (SCRT) with immediate surgery or long-course radiotherapy (LCRT) combined with concurrent fluoropyrimidine-based chemotherapy and delayed surgery based on multi-disciplinary review [81]. Prior to the pandemic, the preferred approach in the USA was LCRT primarily due to concerns among providers for less tumor downsizing and increased toxicity with SCRT, albeit in the absence of randomized data [82]. However, in the pandemic setting, experts recommended pursuing shorter courses of radiation to reduce COVID-19 exposures and still maintain comparable survival benefits.

The non-inferiority Stockholm III trial suggested that recurrence outcomes were similar between SCRT (5 × 5 Gy radiation) with surgery within 1 week, SCRT with surgery after 4–8 weeks, and LCRT (25 × 2 Gy) with surgery after 4–8 weeks [83]. Comparable outcomes with short courses of pre-operative radiation were also demonstrated in other studies [84–86]. In addition, pathologic complete response rates were higher in SCRT patients who delayed surgery without significant differences in sphincter preservation and R0 resection rates [87]. The GRECCAR-6 trial reported extending the time from completion of radiotherapy to surgery from 7 to 11 weeks did not influence overall survival (OS), disease-free survival, distant recurrences, or local recurrences [88]. Promising results with neoadjuvant SCRT in combination with chemotherapy and immunotherapies were also seen in the RAPIDO trial and a phase II study, respectively, presented at the American Society of Clinical Oncology (ASCO) 2020 meeting [89•, 90]. Accordingly, expert consensus groups have recommended pursuing SCRT over LCRT and consideration of delaying surgery for definitive treatment during the COVID-19 pandemic in an effort to maintain treatment outcomes, treat more patients at a time, decrease linear accelerator usage, and simultaneously minimize the risks of patient and staff exposures to

COVID-19 [63, 91] (Table 1).

An English National Health Service (NHS) study showed in April 2020 that the monthly proportion of SCRT to LCRT was 63% vs. 32% which had dramatically reversed compared to 2019 patterns when it was 19% vs. 70%, respectively [33]. In the USA, some cancer centers published their experiences and mandated all patients with locally advanced rectal cancer be treated with SCRT during the pandemic and even consider SCRT with total neoadjuvant therapy off-trial [92]. The current recommendations leading to increased use of SCRT in the USA may result in increased familiarity among providers, and it will be interesting to see if this leads to changes in treatment practices that last beyond the pandemic.

Surgery

The American College of Surgeons developed COVID-19 guidelines in March 2020 to triage surgical care depending on urgency of surgery, number of COVID-19 cases, and availability of hospital resources [93]. When resources were limited, routine and elective surgeries were deferred and attempt to delay surgery that would provide survival benefit with initiation or prolonging of neoadjuvant therapy where feasible was recommended. Patients with obstruction, perforation, bleeding, or impending complications were prioritized for surgery and alternatives such as diverting stomas and locoregional therapies like radiation were recommended if feasible.

The complications and risks of operating on patients during a pandemic also had to be considered. Doglietto et al. demonstrated a 9.5-fold increased risk of 30-day mortality and a 5-fold increased risk of complications in COVID-19 infected patients undergoing surgery compared to uninfected surgical patients [94]. A 35-fold higher risk of pulmonary complications and 13-fold higher risk of thrombotic complications were also noted. A meta-analysis reported a high global post-operative mortality rate of 20% in COVID-19 patients [95]. While peri-surgical mortality in infected patients is demonstrated, other studies suggest the risks of contracting COVID-19 or increased mortality when operating on non-infected patients are less concerning. A French multi-center cohort study of 448 patients who underwent colorectal and anal cancer resection between January 1, 2020, and March 31, 2020, and returned to the pandemic environment reported an infection rate of 1.3% and no deaths until June 15, 2020 [30]. Based on the reassuring infection rate, the authors suggested there was no additional COVID-19-related mortality in patients having undergone CRC surgery. Similarly, an Italian study suggested that major CRC surgery during the COVID-19 pandemic in unaffected patients had comparable complication rates compared to pre-COVID-19 procedures [96]. It is important for multidisciplinary teams to discuss these considerations with patients when determining an optimal time for surgery while not compromising on survival outcomes especially in the curative setting.

Local and locoregional CRCs are associated with 5-year OS rates of 90% and 72%, respectively, which far exceed the more dismal 14% survival rate when metastatic [9]. Given the survival benefit with curative-intent surgery, expert groups strongly recommended pursuing definitive surgery and avoiding delays over 6 weeks from diagnoses which may be associated with inferior survival

outcomes [59, 97]. In the oligometastatic setting, the EORTC 40983 trial demonstrated a progression-free survival benefit when 6 cycles of FOLFOX were given before and after surgery compared to surgery alone [98]. Since most of these patients start with systemic therapy with the goal of controlling disease, downsizing tumors, or bridging to surgery, curative-intent oligometastatic resection timing tends to be more flexible. If tolerated, physicians may prolong neoadjuvant therapy to allow delays in surgery if resource limitations or safety concerns are present. As previously described, we advocate that locally advanced rectal cancers still undergo neoadjuvant therapy with a multi-disciplinary approach to determine the safest timing for surgery as delaying resection even up to 12 weeks may be acceptable without compromising survival benefit [83, 88].

Not surprisingly, the pandemic has led to decreased rates of CRC surgeries globally. The NHS England study revealed a 31% relative reduction in CRC operations by April 2020 compared to 2019 operations [33]. Another international survey demonstrated that CRC surgery was delayed in 58.3% of divisions globally with 90% of delays ranging 5 to 8 weeks beyond normal wait times [99]. Grass et al. used the American College of Surgeons National Cancer Database to demonstrate that delaying surgery beyond 40 days in resectable CRC negatively impacted OS [97]. Larson et al. used this data in the context of COVID-19 and predicted the death of an additional 10,000 Americans over a 5-year time period if CRC surgeries in stage I–III patients were delayed over 4 months [100]. We will inevitably learn more about the consequences of delayed procedures in select populations in the upcoming months to years.

Management of COVID-19 infections

The ASCO and National Comprehensive Cancer Network (NCCN) have released general recommendations for management of patients under investigation (PUI) for COVID-19 and for those who test positive [101, 102]. PUIs should delay cancer treatments and infusion center visits until their test results return, and if positive, referral to the emergency department versus at-home quarantine should be made at the discretion of the provider. For those that have confirmed infection, infusion services and cancer-directed therapy should be delayed at least 10 days from symptom onset or first positive RT-PCR test, and patients should have improvement of symptoms with 24 h without a fever in the absence of antipyretics prior to returning the infusion center or restarting cancer therapy. A study by Liu et al. suggested that mild to moderate COVID-19 cases have early viral clearance around day 10 post-symptom onset, but severe cases have longer infectivity that can last beyond 20 days post-symptom onset [103]. Therefore, assessing the severity of infection and immunosuppression can help determine the length of recommended isolation and treatment delay. For severely immunocompromised individuals, the CDC suggests a test-based approach in symptomatically improved patients with two consecutive RT-PCR tests over 24 h apart and consultation with infectious disease prior to discontinuing isolation procedures [104]. Recommendations for patients with significant COVID-19 exposures are also outlined by the NCCN [101].

Following the Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs), high-risk outpatients including those with active cancer and immunosuppression with mild to moderate symptomatic COVID-19 infections

could be considered for antispike neutralizing monoclonal antibodies bamlanivimab with or without etesvimab or casirivimab and imdevimab although the trials supporting their use do not detail the number of cancer patients included [105–108]. The antiviral remdesivir can be considered for those hospitalized with COVID-19 pneumonia with hypoxia but not yet requiring mechanical ventilation or extracorporeal membrane oxygenation, and glucocorticoids can also be considered although with unclear benefit in neutropenic and immunosuppressed patients [109–111]. Kalil et al. conducted a trial showing that baricitinib, an inhibitor of Janus kinase 1 and 2, in addition to remdesivir can be considered when glucocorticoids are contraindicated [112]. However, the baricitinib plus remdesivir arm only had 20 cancer and 17 immunocompromised patients out of 515 total patients, and the remdesivir control arm only had 17 cancer and 13 immunocompromised patients out of 518 total patients. In addition, convalescent plasma can be considered for hospitalized patients as there are some data supporting its use especially in those unable to mount an adequate humoral immune response [113, 114]. The NCCN guidelines provide more detailed rationale when considering these treatments [101]. Overall, we currently lack strong efficacy data of these treatments in cancer patients due to low numbers of oncology patients studied.

Finally, it is important to consider COVID-19 testing when working up neutropenic fever, a diagnosis commonly encountered in oncology patients. These patients should still be appropriately covered empirically with antibiotics. Oncologists should continue to use the ASCO and Infectious Diseases Society of America (IDSA) guidelines to evaluate which patients are appropriate for outpatient management with oral antibiotics to potentially minimize hospital exposures and which patients need prompt hospital admission for intravenous antibiotics and workup [115]. Extreme caution is advised when considering the use of granulocyte colony-stimulating factor (GCSF) in neutropenic patients with active COVID-19 infections. A few cases have reported rapid clinical deterioration after introducing GCSF in COVID-19 patients possibly attributed to the rise in cytokines and increased risk of capillary leak syndrome [116–118].

COVID-19 vaccination

On December 11, 2020, the FDA issued an EUA for the first COVID-19 mRNA vaccine made by Pfizer-BioNTech for emergency use. Since then, on December 18, 2020, and February 27, 2021, it granted EUAs for an mRNA vaccine by Moderna, Inc., and a viral vector vaccine by Janssen Biotech, Inc., respectively. The initial vaccine roll-out was challenging with limited availability, but now the rate of vaccination with the three authorized options on the market rises daily. The NCCN recommends cancer patients and their close contacts get vaccinated with any of the three vaccines whenever one becomes available to them [119].

We counsel patients on the efficacy and safety of the vaccines in the general population but review that the effectiveness and toxicities in cancer patients are not currently known as immunosuppressed patients and those on immune-modulating drugs were excluded from the vaccine trials [120–122]. Prior studies suggest that other inactive vaccines are safe in cancer patients and still have efficacy even if patients are on chemotherapy although relative efficacy may vary based on tumor type [123, 124]. The current COVID-19 vaccines also do not contain live or functional virus and

thus are not expected to cause active infection in immunocompromised patients. Extrapolation from prior vaccine studies, IDSA guidelines, and the published COVID-19 vaccine studies supports the recommendation for patients to pursue vaccination as soon as possible while still carefully adhering to prevention guidelines [125].

The optimal timing of vaccination in relation to chemotherapy or immunotherapy cycles is unknown. An influenza vaccine study including breast and lung cancer patients receiving cytotoxic chemotherapy on a 3-week schedule reported comparable antibody responses between vaccinated patients on day 1 or day 11 during a cytopenic period of the cycle [126]. However, in practice, there are a myriad of regimens with different combinations of therapies, dosing levels, and degrees of myelosuppression. As many physicians believe corticosteroids that exceed physiologic doses may blunt vaccine immune responses, it may be reasonable to avoid vaccination within a few days of chemotherapy infusion if premedications include high-dose steroids. If feasible, oncologists may recommend adjusting the timing of vaccinations or rescheduling treatment infusions to avoid overlapping toxicities especially in highly symptomatic patients. The COVID-19 and Cancer Clinical Trials Working Group have also issued guidance on vaccination timing around clinical trial screening and advocates for including vaccinated patients in clinical trials that normally lists the use of other "investigational therapies" as an exclusion criteria [127]. In addition, the FDA clarified that the vaccines given under EUA are not considered "investigational products" [128]. Updates to efficacy, safety, and guidance for revaccination or boosters after immunosuppressive therapies will be issued as we learn more about the vaccine in cancer patients. For instance, the ongoing phase 3 "vaccination against COVID in cancer" (VOICE) trial will assess whether chemotherapies or immunotherapies affect how patients respond to mRNA COVID-19 vaccinations [129].

Summary

We are all eager for the pandemic to be over; none more than our patients. As our patients have had to stay away from friends and family and their critical emotional support systems, we know that they are suffering more than many. CRC care is a multi-disciplinary activity, and while we have been able to maintain interactive collaboration through remote conferencing, we, too, perform better when we are together. The COVID-19 pandemic forced us to make dramatic changes, many of which are for the better. Several lessons have been learned, reshaping our future practice. The stress of this event has left our medical community stronger and more focused. Our success will be measured by the mortality rates of CRC over the next several years.

Declarations

Conflict of Interest

Reetu Mukherji declares that she has no conflict of interest. John L. Marshall declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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