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Colorectal Cancer Chemotherapy during COVID-19 Pandemic

Abstract

The management of patients with colorectal cancer during the current SARS-CoV2 pandemic opens a Pandora's Box. While the world is facing an unprecedented crisis of fighting a life-threatening infectious disease, patients with colorectal cancer are facing the dual challenge to fight cancer while protecting them from infection. We attempted to critically examine the existing evidence for chemotherapy in colorectal cancer in different stages of disease and suggest treatment options in these vulnerable patients. Treatment options which do not overburden existing health-care resources can be provided for patients with colorectal cancer patients requiring chemotherapy without significant compromise in efficacy or increase the risk of hospital acquired SAR-CoV-2 infection.

Keywords: *Chemotherapy, colorectal cancer, COVID-19, SARS CoV2*

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Introduction

Colorectal cancer is one of the five most common cancers worldwide and in India.[1] The onset of SARS-CoV-2 pandemic worldwide had led to a lockdown in many parts of the world, with more than 1.2 million people affected and 65,000 deaths reported at the time of writing this article. The pandemic is expected to grow further affecting most of the countries. The management of patients with colon cancer needs to be re-evaluated without overburdening the existing health-care resources. The benefit of anti-cancer treatment should be weighed against the risk of infection with SARS-CoV-2 due to hospital visits. Cancer patients are at a high risk of adverse outcomes (need for hospitalization, admission to intensive care units) and death from SARS-CoV-2.[2] The presence of comorbidities such as cardiovascular diseases, hypertension, diabetes, chronic respiratory illness worsens the outcome of SARS-CoV-2 infection [Table 1].[3] Age is another risk factor and the risk of mortality based on age is presented in Table 2.[4] We attempt to re-evaluate existing evidence and formulate a treatment strategy in colorectal cancer to decrease risk of infection during this pandemic without compromising oncological outcomes.

Adjuvant Chemotherapy in Colon Cancer

The absolute benefit of adjuvant chemotherapy is 5% in resected colon cancer.[5] However, the benefit varies based on the stage of the disease and clinicopathologic features. Patients with stage 1 are advised only observation. Benefits of chemotherapy based on stage and age are summarized in Table 3.

High Risk Stage 2 Colon Cancer

High risk features in a resected Stage 2 colon cancer include T3/T4 disease,[6] <12 lymph nodes resected in surgical specimen, poorly differentiated adenocarcinoma, lymphovascular invasion and perineural invasion, obstruction or perforation at presentation. However, all these high-risk features have differential impact on outcome. Patients with high microsatellite instability (MSI-H) do not benefit from single-agent fluoropyrimidine-based chemotherapy.[7] However, MSI-H patients with T4 disease may require oxaliplatin-based chemotherapy

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regimen.[7] Patients with microsatellite stable disease (MSS) and with T4 disease or more than one risk factor can be considered for oxaliplatin-based chemotherapy. We recommend oral capecitabine and oxaliplatin combination therapy (CAPOX) in this setting due to decreased hospital admission duration and decreased hospital visits as compared to infusional 5-fluorouracil (5-FU)-based regimen The recent IDEA meta-analysis in high risk Stage 2 colon cancer, which included 4 randomized controlled trials, showed 3-month duration of chemotherapy is as effective as 6 months especially when CAPOX (5 years disease-free survival [DFS] 82% vs. 81.7% for 6 months vs. 3 months) is used as the regimen.[8] While the noninferiority did not reach statistical significance, the marginal decrease in absolute benefit does not outweigh the risk of adverse outcomes in these extraordinary situations. In patients with high risk Stage 2 MSS disease we recommend 6 months of oral capecitabine or 3 months of CAPOX regimen, wherever applicable. In patients receiving combination chemotherapy, the maximum benefit is conferred with 5-FU/oral capecitabine as compared to oxaliplatin. In resource constrained setting, we would strongly recommend 6 months of oral capecitabine in these patients.

Stage 3 Low Risk (T1-T3 and N1) Colon Cancer

Recent IDEA meta-analysis and meta-analysis by Boyne *et al*. (which included randomized and nonrandomized trials) showed that patients with low risk Stage 3 (T1–T3, N1) had non inferior outcome with 3 months of adjuvant CAPOX chemotherapy.[9] Patients already on oxaliplatin-based regimen can receive 3 months of adjuvant chemotherapy without compromising long-term outcome.[9,10] However, among the two active agents, 5-FU/oral capecitabine adds substantial benefit to surgery as compared to oxaliplatin. Hence, in resource constrained situations, oral capecitabine is strongly recommended in these patients and resumption of oxaliplatin in subsequent cycles for a total of 4 cycles may be an optimum strategy in these circumstances despite lack of Level 1 evidence.[11]

Table 1: Risk of death/intensive care admission/ mechanical ventilation due to comorbidities in severe acute respiratory syndrome-coronavirus 2 pandemic

	HR for composite end point	95% CI
Type of co morbidities		
COPD	2.681	1.424-5.048
Type 2 diabetes mellitus	1.586	1.028-2.449
Hypertension	1.575	1.069-2.322
Active malignancy	3.501	1.604-7.643
Age	1.030	1.022-1.050
Smoking	1.668	1.006-2.764
Number of comorbidities		
1	1.789	1.155-2.772
2 or more	2.592	1.611-4.171

CI – Confidence interval; COPD – Chronic obstructive pulmonary disease; HR: Hazard ratio

Stage 3 High-Risk (T4 or N2 Disease) Colon Cancer

These patients require 6 months of adjuvant chemotherapy. It is preferable to use CAPOX regimen over FOLFOX due to the shorter infusion time, decreased frequency of visits (3 weeks vs. 2 weeks), and duration of hospital stay (4 h vs. 48 h) with similar benefit. The time to recurrence in this subgroup of patients is 14 months according to ACCENT database,[12] and hence, we strongly recommend continuing chemotherapy in these patients for a total duration of 6 months. An informed decision needs to be taken after discussing the risks and benefits of chemotherapy in the background of the pandemic with the patient and their caregiver (s). In high risk (T4/N2), most of the benefit is already achieved with 4 cycles of CAPOX so in extenuating circumstances, an individualized risk-benefit decision may be taken for continuing 4 more cycles. The hazard ratio for recurrence in T4/N2 is only 1.12 and the number needed to treat to reduce one extra recurrence is 59.[13] In case of significant health system strain and risk of COVID-19 infection, the patient can switch to oral capecitabine alone after 4 cycles CAPOX.

Adjuvant Chemotherapy in Rectal Cancer

Adjuvant chemotherapy in rectal cancer has always been debated in terms of benefit. However, the principles of adjuvant chemotherapy may not vary between colon cancer and rectal cancer.

Patients with a good response (defined as pathological complete response and down staging to ≤ ypT2 and node negative disease) are likely to benefit from adjuvant chemotherapy. This is based on the large data from a retrospective study which showed patients with baseline

Table 2: Age-wise mortality rates with COVID-19

Age (years old)	Death rate confirmed cases (%)	Death rate in China (%)	Death rate in Italy (%)
80+	21.9	14.8	20.2
70-79		8.0	12.8
60-69		3.6	3.5
50-59		1.3	1.0
40-49		0.4	0.4
30-39		0.2	0.3

Table 3: Benefit of adjuvant chemotherapy in resected colon cancer based on stage and age

Average benefit of adjuvant 5-fluorouracil (high-grade Stage 2) percentage of patients alive due to chemotherapy after 5 years			
Stage	**Age**		
	30-40 (%)	**40-60 (%)**	**60-80 (%)**
T3N0	2.2	2.2	1.9
Average benefit of adjuvant FOLFOX percentage of patients alive due to chemotherapy after 5 years (T4 disease and stage 3)			
T4N0	3.9	3.9	3.4
T3N1	16.9	16.6	14.4
T3N2	24.5	24.1	20.9
T3N3	26.7	26.3	22.9
T4N1	21.9	21.5	18.7
T4N2	27.5	27.1	23.6
T4N3	18.9	18.6	16.1

Data compiled using onco-assist application endorsed by ESMO

clinical T3/4 disease and lymph node positive disease who achieved pathological complete response benefitted most from adjuvant chemotherapy.[14] Meta-analysis by Maas *et al*. showed significant benefit from adjuvant chemotherapy in patients achieving ypT1–T2 postneoadjuvant chemoradiation.[15] Most of the studies in this meta-analysis used single-agent fluoropyrimidine as adjuvant chemotherapy. Since oral capecitabine monotherapy obviates the need for hospital admission, we would suggest oral regimen in these patients without affecting long-term survival.

Patients with no or minimal response to neoadjuvant chemoradiation (ypT3/T4 and node positive) would benefit from oxaliplatin-based chemotherapy. Meta-analysis by Zhao *et al*. showed the maximum benefit from combination chemotherapy in this setting.[16] However, there was no benefit in overall survival with further need for longer follow-up. In view of high risk of death due to disease in these nonresponders (68% vs. 57% in patients receiving adjuvant chemotherapy), there is a strong reason to use oxaliplatin-based combination chemotherapy.[17] Similar to patients with high risk Stage 3 colon cancer, these patients should be treated with CAPOX-based chemotherapy which decreases the need for hospital visit and duration of hospital stay.

Neoadjuvant Chemotherapy in Colon Cancer Patients Awaiting Surgery

Patient with potentially resectable disease but deferred surgery due to resource constraints which includes transport, availability of hospital beds and personal protective equipment supply, and risk of infection in the perioperative period can be started on neoadjuvant chemotherapy. The recent FOxTROT study examined the role of neoadjuvant chemotherapy in resectable colon cancer which showed histological regression in 59% of patients.[18] There was decreased rate of incomplete resection in patients with cT3/T4 disease without the risk of disease progression in this study, though there was no improvement in DFS. Oxaliplatin-based regimen preferably CAPOX can be used in patients awaiting curative surgery.

Metastatic Colorectal Malignancy

Newly diagnosed patients with metastatic disease can undergo chemotherapy with CAPOX regimen along with biological agents. Irinotecan-based regimens, which use infusional 5-FU, require prolonged hospitalization and frequent visits, can be avoided. If infusional regimen is used, portable pump can be used to decrease the duration of hospitalization.

Biological agents (cetuximab, panitumumab, and bevacizumab) add incremental survival benefit when added to chemotherapy. Anti-epidermal growth factor receptor agents cetuximab or panitumumab have demonstrated survival benefit with only infusional 5-FU regimen in left-sided RAS wild type colon cancer. An informed decision should be taken after discussing the risks and benefits of infusional regimen and need for frequent hospital visits with patient and their caregiver (s). Portable pumps which reduce the duration of hospitalization can be used when infusional regimen is given. Patients with right-sided tumor and left-sided tumor with RAS mutation bevacizumab is the preferred biological agent which can be used with CAPOX regimen.

Patients with metastatic disease and who previously received oxaliplatin-based regimen can be considered for modified capcitabine and irinotecan or tegafur, leucovorin and irinotecan (1:4 molar combination of ftorafur with uracil, leucovorin and irinotecan) rather than infusional 5 FU and irinotecan-based regimen (FOLFIRI).[19] A phase 2 study by Shigeta *et al*. showed similar progression free survival with both TEGAFIRI and FOLFIRI regimen (9.9 months vs. 10.6 months).[20] The use of third or more line (e.g., checkpoint inhibitors, anti-Her2 therapy, anti-BRAF) should be done extremely judiciously on case by case basis explaining the risks and chances of benefit. Palliative surgery for perforation and obstruction may be done while biopsies of metastatic lesions should be minimized and liquid biopsy used.

Patients with poor performance status and not fit for intensive chemotherapy should be encouraged for home-based care or single agent oral fluoropyrimidine (capecitabine, UFT), if feasible. In general, the bolus part of modified FOLFOX 6 may be omitted and the infusional 5FU continued, in an attempt to minimize neutropenia. In the metastatic setting, cycles may be delayed judiciously to decrease the frequency of visits. Granulocyte colony stimulating factors may be used liberally in patients with previous or expected toxicity.

UFT-based combination regimen with either oxaliplatin or irinotecan along with or without biological agent has

Table 4: Summary of suggested modifications in the management of colorectal cancer

	Treatment options	Suggested alternatives
Adjuvant chemotherapy in colon cancer		
High risk stage 2		
MSI-H pT4 only	CAPOX 3 months	Observation or 3 months CAPOX
MSS	SA Capecitabine/CAPOX/FOLFOX	Oral Capecitabine for 6 months (preferred)/no >3 months CAPOX
Low risk stage 3	CAPOX 3 months	CAPOX 3 months
	FOLFOX 6 months	Oral capecitabine (6 months)
High risk stage 3	CAPOX 6months	CAPOX 6 months
	FOLFOX 6 months	Oral Capecitabine 2 cycles f/b CAPOX 6 cycles
Elderly patients	SA capecitabine	Oral capecitabine
Adjuvant chemotherapy in rectal cancer		
Good responders (pCR, ypT1-2)	CAPOX	Oral capecitabine
	FOLFOX	
	SA Capecitabine	
Poor responders	CAPOX	CAPOX 3months
	FOLFOX	Oral Capecitabine 6 months
Metastatic colorectal cancer		
Treatment naïve	CAPOX	CAPOX
	FOLFOX	Modified XELIRI
	FOLFIRI	TEGAFOX
		TEGAFIRI
Postoxaliplatin-based chemotherapy regimen	FOLFIRI	Modified XELIRI
		TEGAFIRI

shown similar efficacy to infusional regimen.[21-24] The data for UFT-based combination chemotherapy in this setting are from Phase 2 studies; however, it is safer alternative when the risk of SARS-Cov2 infection and complications is high in the current situation.

Patients who attained partial response after certain cycles of chemotherapy can be advised maintenance therapy with oral capecitabine.[25] Biological agents may be withheld for few cycles after explaining the risk and benefits of such approach during pandemic to patient and their caregiver (s). Table 4 summarizes the treatment suggestions based on the existing evidence depending on stage and clinical scenario. ESMO guidelines for the management of CRC in COVID19 pandemic are a useful resource in this setting and we agree with most of the recommendations. All the "high-priority" interventions should be given precedence over the "medium and low priority" ones.[25] All treatment including first line for patients with poor performance status, heavy comorbidities, slow growing recurrent disease and those patients who had severe complications during the adjuvant therapy should be delayed.

Apart from these specific recommendations, general principles such as social-distancing in the outpatient departments, cough etiquettes, increased use of telemedicine to decrease hospital visits should be followed and explained to colorectal cancer patients.

The use of chemotherapy in the management of colorectal cancer during SARS-CoV2 pandemic requires prudent use of health-care resources and existing evidence. With prospects of clinical trials in these situations being difficult to conduct to give definitive evidence we attempted to derive the rational protocols from the existing data to formulate optimum treatment strategy without significantly deviating from the evidence.

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Conflicts of interest

There are no conflicts of interest.

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