



ESMO management and treatment adapted recommendations in the COVID-19 era: colorectal cancer

Loredana Vecchione ^{1,2}, Sebastian Stintzing ³, George Pentheroudakis,⁴ Jean-Yves Douillard,⁵ Florian Lordick ⁶

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¹Charite Comprehensive Cancer Center, Charite Universitätsmedizin Berlin, Berlin, Germany

²Department of Hematology, Oncology and Tumor Immunology (CCM), Charite Universitätsmedizin Berlin, Berlin, Germany

³Medical Department, Division of Oncology and Hematology, Charite Universitätsmedizin Berlin, Berlin, Germany

⁴Department of Medical Oncology, University of Ioannina, Ioannina, Epirus, Greece

⁵European Society for Medical Oncology, Viganello, Switzerland

⁶Department of Oncology, Gastroenterology, Hepatology, Pulmonology and Infectious Diseases, Leipzig University Medical Center, Leipzig, Germany

Correspondence to

Professor Florian Lordick;
florian.lordick@medizin.uni-leipzig.de

ABSTRACT

COVID-19 pandemic challenges health system capacities in many countries. National healthcare services have to manage unexpected shortage of healthcare resources that have to be reallocated according to the principles of fair and ethical prioritisation, in order to maintain the highest levels of care to all patients, ensure the safety of patients and healthcare workers and save as many lives as possible. Beyond that, cancer care services have to pursue restructuring, following the same evidence-based dispositions. In this article, we propose guidance to the management of colorectal cancer during the pandemic, prioritised according to a three-tiered framework, based on expert clinical judgement and magnitude of benefit expected from specific interventions. Since the availability of resources for diagnostic procedures, surgery and postoperative care, systemic therapy and radiotherapy may differ, authors did separate prioritisation analyses. The impact of postponing or abrogating cancer interventions on outcomes according to a high, medium or low priority scale, is outlined and discussed. The implementation of healthcare services using telemedicine is explored: it reveals itself as functional and effective for limiting patients' need to travel to centres and thereby has the potential to reduce diffusion of severe acute respiratory syndrome coronavirus 2. Colorectal cancer demands a considerable amount of medical resources. Therefore, the redefinition of its diagnostic and therapeutic algorithms with a rigorous method is crucial in order to ensure the highest quality of continuum of care in the broader context of the pandemic and the challenged healthcare systems.

INTRODUCTION

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The novel virus was first identified in a cluster of patients with atypical pneumonia in Wuhan, China, in December 2019.¹ COVID-19 is associated with presentations ranging from asymptomatic infections to severe viral pneumonia, acute respiratory distress syndrome, multi-organ failure and death.² As of 5 May 2020, a total of 3 517 345 confirmed cases and 243 401 confirmed deaths have been reported across >150 countries.³ With such high numbers of critically ill patients and rapidly increasing numbers of newly diagnosed patients,

hospitals throughout the world have been overwhelmed, thus posing an unprecedented challenge to healthcare systems. Indeed, this has required a rapid development of reliable and evidence-informed recommendations for the priority setting of healthcare services. Furthermore, it has led to an urgent identification of non-COVID health priorities.⁴ So far, we know that individuals ≥60 years of age and/or those with a suppressed immune system and comorbidities such as cardiovascular diseases, diabetes and chronic respiratory insufficiency are particularly vulnerable to a severe course of COVID-19.

Patients with cancer often need to leave their homes and visit the hospital for cancer treatment, check-ups and the management of cancer-related or treatment-related complications.^{5–8} Often, they also require home assistance from palliative healthcare teams or simply from their family members. Moreover, patients with cancer are often in an immunosuppressed state because of the disease itself or the cancer treatment. Finally, a majority of patients with cancer are older than 60 years which has been identified as a risk factor for COVID-19 severe course by itself.

This has therefore led oncology societies and national authorities to issue guidelines on cancer care during the COVID-19 pandemic. While oncologists are accustomed to dealing with infections in cancer, the problem with COVID-19 is that there is no specific treatment. On one hand, patients with cancer might be at high risk of having severe complications during potential COVID-19 infection, but on the other hand, patients might be at high risk of cancer progression and death if not appropriately treated. In that respect, oncologists need to assess if a treatment plan should start or should be delayed and if delayed for how long. Without scientific evidence and with the pandemic evolving rapidly in many parts of the world, it is challenging to write robust evidenced-based guidelines. Nevertheless,



European Society for Medical Oncology (ESMO) as well as other cancer organisations tried to summarise recommendations for cancer patients' management in the COVID-19 era based on expert opinions.

Based on the UNESCO working definition, the precautionary principle dictates that 'when human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm'.⁹ This principle can be applied to treatment recommendations for patients with cancer during the pandemic.

The current work aligns in parallel to WHO recommendations¹⁰ and summarises the expert recommendations for cancer treatment management in the COVID-19 pandemic for patients with colorectal cancer (CRC).

Methodology for the selection of priority interventions

The present manuscript is the result of an international panel of expert health providers in the management of CRC and is proposed to guide healthcare professionals treating patients with CRC during the COVID-19 pandemic. The expert consensus-based recommendations are not intended to replace the current guidelines. In contrary, they are meant to guide clinicians to set priorities and adapt CRC care during the COVID-19 pandemic, using a value-based framework. All the adaptations and prioritisations have been discussed between the experts via emails contact until consensus was reached.

In order to provide a framework for the medical community to treat cancer during the COVID-19 pandemic, the ESMO established a guidance for clinicians, defining three levels of priorities regarding medical interventions, namely: tier 1 (high priority intervention), 2 (medium priority) and 3 (low priority)—informed by the Ontario Health Cancer Care Ontario framework of resource-prioritisation and by the ESMO Magnitude of Clinical Benefit Scale, a public health tool intended to support the uptake of medical interventions in oncology.^{11 12}

Overall, the prioritisation has been developed to incorporate both the information on the value-based prioritisation and clinical cogency of the interventions:

- ▶ **Tier 1, high priority:** patient condition is immediately life threatening, clinically unstable and/or the magnitude of benefit qualifies the intervention as high priority (eg, significant overall survival (OS) gain and/or substantial improvement in quality of life (QoL)).
- ▶ **Tier 2, medium priority:** patient situation is non-critical but delay beyond 6 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority.
- ▶ **Tier 3, low priority:** patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (eg, no survival gain with no change nor reduced QoL).

The clinical guidance defined by ESMO must be interpreted in the broader context of healthcare response to

the pandemic, and always linked to the Global Norms of WHO, the lead public health Agencies and health technical governmental boards, for the definition of the strategies for the preparedness and response on populations—including the interventions to ensure the safest conditions for the health workforce, the proper provision of personal protective equipment, the testing strategy for healthcare personnel, patients and communities. Inconsistencies of clinical guidelines developed outside the global strategy and not in coordination with the strategic population policies of pandemic control will inevitably harm communities, with the earliest impact being on the most vulnerable patients—patients with cancer being first among them.¹¹

Reorganising the outpatient setting and visit priorities for patients with CRC

In an era in which no validated active treatments or vaccines against SARS-CoV-2 haven been approved yet in the European community and beyond, it is clear that the spread of SARS-CoV-2 may only be controlled by reducing the exposure to the virus, thus keeping physical distancing. Therefore, the care of patients with cancer, who are at higher risk of infection and especially complications as compared with the overall population, need to be reorganised at different levels by considering the priorities as reported above. It is of utmost importance that every single treatment decision is made by a multidisciplinary team and shared with the patient. The patient needs to be fully informed of all the risks and benefits he/she can expect from any medical intervention in the context of the current public health crisis. We, as healthcare providers, need to make sure that patients understand the potential risks as much as possible and that the decisions are made based on an informed consent. The outpatient setting represents one of the places where the risk of infection might be higher as compared with other settings, simply because the number of accesses per day is high and patients might not only come for treatment but also for simple follow-up or controls of side effects. In this respect, hospital visits should be reduced. For CRC, patients considered as requiring high priority outpatient visits are those with potentially unstable conditions such as acute abdominal pain, intestinal occlusion, symptomatic ascites, complications after surgery/endoscopy or radiological interventions, acute or chronic diarrhoea, severe skin toxicity, new symptoms, clear clinical progression and deterioration (**box 1**). For specific conditions resulting from treatment-related toxicities, such as febrile neutropenia with adverse prognostic factors, a rapid clinical intervention can make a difference in the prognosis as well as optimise the treatment delivery plan, thus must be included in the priorities.¹³

Medium priority patients are, for example, those under treatment or who should start a treatment. In that respect, it is now more than ever important to define the best therapeutic option based on the tumour biology, patients' comorbidities, clinical benefit (OS vs reduction

Box 1 Priorities for patients with colorectal cancer (CRC): outpatient visit priorities

High priority

- ▶ Potentially unstable (acute abdominal pain, intestinal occlusion, ascites, complications after surgery/endoscopy or radiological interventions, diarrhoea, severe skin toxicity, new symptoms, clinical progression).
- ▶ Symptomatic new patients (symptomatic ascites, intestinal occlusion, chronic diarrhoea).

Medium priority

- ▶ Newly diagnosed asymptomatic patients, no prior surgery.
- ▶ Newly diagnosed asymptomatic patients after surgery for treatment strategy planning in case of adjuvant and first-line treatment.
- ▶ Chemo/radiotherapy-related serious side effects.
- ▶ Established patients with new problems or symptoms from treatment—convert as many visits as possible to telemedicine appointments.

Low priority

- ▶ Second opinion.
- ▶ Secondary prevention of CRC; if possible, schedule blood tests and imaging close to home and convert to telemedicine.
- ▶ Follow-up visit out of study.
- ▶ Restaging in metastatic setting when the goal is not to perform surgery with curative intent on metastatic and primary lesions.
- ▶ Restaging in third-line and fourth-line treatment.
- ▶ Follow-up visit on maintenance treatment; if possible, schedule blood tests and imaging close to home and convert to telemedicine.

of the symptoms) expected and the possibility to reduce as much as possible the hospital visits to reduce the risk of exposure to the virus. In that respect, quality of care should be kept unchanged despite of the prioritised interventions. This means that the treatment planning of patients with CRC should always follow a multidisciplinary board discussion. While the format of such discussion might change, like videoconferencing, the principle of multidisciplinary care is not negotiable.¹⁴

Overall, triaging patients for fever and other COVID-19-related symptoms is mandatory and an entry checkpoint should be considered by all healthcare facilities. Patients should avoid to visit the outpatient clinics in the presence of family members unless strictly necessary.

Importantly, patients with fever should not be evaluated in the outpatient clinic, but the initial evaluation should be rather done in dedicated areas with low concentration of patients with cancer and oncology staff. In the presence of fever, only after the exclusion of positivity to COVID-19, patients should be transferred to the cancer centre. Patients with mild symptoms testing positive for COVID-19 should not access the cancer centre to avoid contagious dissemination, while a delay of their therapy should be discussed with the attending oncologist. COVID-19 negative patients with fever but in stable conditions could receive oral antibiotic treatment at home. Telemedicine can help to monitor them and identify in advance the group of patients who might require hospitalisation due to the development of complications.

Specifically, for patients with cancer receiving intravenous treatment with 5-fluorouracil (5-FU) the switch to oral capecitabine should be considered, independently from the stage of the disease and the line of treatment. For those patients who are receiving oral treatments (eg, chemotherapeutics like capecitabine alone or trifluridine/tipiracil (TAS-102) and biological agents such as regorafenib) outpatient appointments can be replaced by web technology contacts. While it is important to ensure the patients about potential side effects and the continuous contact with healthcare providers, it is in those cases possible to avoid visits when not necessary. Additionally, psychological support might be needed. On patients' consent, psychological support might also be provided on web-based platforms.

Finally, second opinion visits, follow-up, blood test controls, staging in metastatic setting especially when no curative surgery is planned and second prevention examinations for CRC are all considered as non-urgent situations. For all those cases telemedicine is an option.

Priorities for imaging and radiological/endoscopic interventions for CRC

All patients with CRC with signs or symptoms of intestinal obstruction, bleeding, perforation, postsurgical complications and postinterventional procedures as well as bone fractures due to metastasis should be promptly referred to the treatment centre. The diagnosis of such complications and the start of a specific treatment should be designated as high priority (box 2).

Endoscopic interventions meant to obtain a histopathological diagnosis of CRC are of utmost importance since they can have an immediate impact on the therapeutic approach. Therefore, both endoscopic interventions meant to make diagnosis of CRC and imaging meant for CRC staging represents a medium priority. For patients with a symptomatic progression or symptomatic

Box 2 Priorities for colorectal cancer (CRC): imaging and radiological/endoscopic interventions

High priority

- ▶ Radiological confirmation of intestinal occlusion, bleeding, perforation, postsurgical complications and postinterventional procedures.
- ▶ Radiological confirmations of bone fractures due to metastasis.

Medium priority

- ▶ Diagnostic imaging/endoscopy for clinically suspected CRC (clinical, biomarkers, family history).
- ▶ Diagnostic imaging/endoscopy for high-risk categories (familial cases of CRC, serrated polyps).

Low priority

- ▶ Secondary prevention of CRC, prefer to perform occult test; if possible, schedule blood tests and imaging close to home and convert to telemedicine.
- ▶ Follow-up visit out of study.
- ▶ Restaging in metastatic setting when the goal is not to perform surgery with curative intent on metastatic and primary lesions.
- ▶ Restaging in third-line and fourth-line treatment.

relapse both endoscopy and imaging are included in the set of inevitable health services. In those cases, a prompt intervention might be life-saving or improve the QOL of patients, thus making worth the admission into the hospital. Despite of the ample variety of clinical presentations, some disease recurrence patterns are more prone to radical approaches from which long-lasting disease-free intervals can be expected. For example, patients with CRC experiencing locoregional disease recurrence or single relapse in the liver or lungs can still be treated with radical intention—with a combination of locoregional treatment, either surgery or radiation therapy, or complementary treatments such as neoadjuvant chemotherapy followed by surgery. In this setting, it is essential to make the appropriate diagnosis and stage and discuss the individual case in an experienced multidisciplinary board. Every decision needs to be shared with the patients, by highlighting the impact of such decisions on survival and QOL.

On the contrary, during the pandemic, restaging of metastatic patients with CRC, especially those patients under late lines of treatment or those for whom the likelihood of receiving a curative surgery is limited, may be postponed by few weeks or months most probably without a harm. A proper risk–benefit estimation may lead to the decision to postpone rather than push in-house examinations. Similarly, secondary prevention may be delayed, if necessary. In particular, blood occult test in faeces as well as imaging might be performed close to home and consultation and communications of the results might be performed using telemedicine. Follow-up of early CRC, especially outside of clinical studies, may also be delayed unless suspicion of relapse requires prompt intervention.

Priorities for CRC surgery

Surgery is a therapeutic approach with major benefits in terms of cancer survival, especially for early-stage patients with CRC. It also represents the only possible therapeutic option of some complications due to CRC progression or endoscopic interventions. Cancer biology, clinical presentation pattern, patients' condition and preferences need to be taken into account to define the priority setting of surgery for patients with CRC (box 3).

The clinical need for intervention is dictated by the risk for serious cancer-related or intervention-related complications. Bowel obstruction, perforation, peritonitis, massive gastrointestinal bleeding, which can be either cancer or intervention related, represent high priorities for surgical intervention. Same is true for post-surgical (such as anastomotic leak) and postcolonoscopy (such as perforation, bleeding) complications as well as spinal cord compression or fractures due to bone metastases.

Primary surgery of early stage CRC should not be postponed for more than 6 weeks. This is due to the risk of bowel occlusion, perforation, bleeding as well as cancer progression. The administration of neoadjuvant treatment for early stage colon cancer, although of potential benefit for small groups of patients,^{15 16} is not a validated

Box 3 Priorities for colorectal cancer (CRC): surgical oncology

High Priority

- ▶ Radiologically confirmed intestinal occlusion in newly diagnosed patients.
- ▶ Bowel perforation, peritonitis.
- ▶ Massive gastrointestinal bleeding.
- ▶ Postsurgical complications (perforation, anastomotic leak).
- ▶ Postcolonoscopy complications (perforation, bleeding).
- ▶ Postinterventional procedure such as liver and lung biopsies (perforation, organ damage, peritonitis, abscess, massive bleeding).
- ▶ Bone fractures with spinal cord compression due to metastasis.

Medium priority

- ▶ Clinical stage I, II and III colon cancer.
- ▶ Clinical stage I rectal cancer.
- ▶ Clinical stage II–III rectal cancer after neoadjuvant treatment.
- ▶ Resection of metastasis in oligometastatic patients with curative intent as front line or after neoadjuvant treatment.

Low priority

- ▶ Early stage rectal cancer after complete radiological response following radiotherapy (watch-and-wait strategy).
- ▶ Prophylactic surgery—for familiar cases of CRC.
- ▶ Biopsy of metastatic lesions for molecular analysis for late-line treatments. Start last-line options and wait until the end of the COVID-19 pandemic for such evaluation. When possible, use liquid biopsies for such analyses rather than biopsies.

and currently recommended approach in CRC treatment guidelines. Stage II and III patients with rectal cancer completing neoadjuvant treatment should receive curative surgery with no major delays. Nevertheless, for those cases in which this is impossible in terms of critical healthcare resources, adding another cycle of neoadjuvant therapy in those patients responding well to therapy may 'protect' the patient from the postponement of surgery and might be appropriate. In contrast, for patients who are not responding to treatment, surgery should be performed as soon as possible, since the risk of losing the chance of getting a curative treatment might be higher than the risk of being infected. Delays of surgical procedures might induce psychological distress. Therefore, psychological support via telemedicine may be offered.

Reconstructive procedures could be postponed since they do not represent a clinical contingency. Also a watch and wait approach might be considered for early stage rectal tumour that obtain a complete radiological response after neoadjuvant treatment. Prophylactic surgery for hereditary CRC (such as Lynch syndrome, familial adenomatous polyposis) as well as biopsies of metastatic lesions for molecular analysis for precision medicine in late lines of treatment might be postponed and performed at the end of the COVID-19 pandemic. For the latest, the use of liquid biopsy might be considered. Finally, as discussed above, patients experiencing single organ and lesions relapses (liver only, lung only, CRC only) should be discussed in a multidisciplinary team to define the benefit of offering an immediate radical surgery excision with benefit in terms of OS and QOL (no side effects or complications from chemotherapy)

Box 4 Priorities for colon cancer: medical oncology—early colon cancer

High priority

- ▶ Severe complications due to the treatment (surgery, radiation, chemotherapy) that require hospitalisation. Avoid outpatient visit appointments and plan with the medical staff, after triage, admission to the ward.

Medium priority

- ▶ Adjuvant treatment for high-risk stage II patients.
- ▶ For stage II patients, molecular testing for microsatellite instability and dihydropyrimidine dehydrogenase are suggested for treatment decisions.
- ▶ Adjuvant treatment for low-risk and high-risk stage III patients. Consider applying capecitabine in combination with oxaliplatin in place of infusional 5-fluorouracil. Moreover consider, based on the International Duration Evaluation of Adjuvant Therapy trial recommendations and based on oxaliplatin-related side effects, administration of treatment for 3 instead of 6 months.

Low priority

- ▶ Weekly blood tests unless clinical conditions and symptoms require them.
- ▶ Radiological evaluation by considering the patients risk/benefit ratio.

versus postponing surgery after a neoadjuvant systemic treatment.

As usual, the discussion about surgical indications must be individualised. Nevertheless, in the context of the COVID-19 pandemic, all decisions need to be properly explained and shared with the patients, assessing the preference and expectations while informing on the threats and advantages of the adapted treatment plans.

Priorities for early stage colon and rectal cancer

Chemotherapy has shown to improve the OS of early-stage patients with CRC. While for colon cancer the use of neoadjuvant treatment is not recognised as a standard of care,^{15 16} for stage II and III rectal cancer neoadjuvant chemoradiotherapy represents a standard of care. Because adjuvant and neoadjuvant treatment have an impact on survival rates, the start of the treatment should

Box 5 Priorities for rectal cancer: medical oncology—early rectal cancer

High priority

- ▶ Severe complications due to the treatment (surgery, radiation, chemotherapy) that require hospitalisation. Avoid outpatient visit appointments and plan with the medical staff, after triage, admission to the ward.

Medium priority

- ▶ Neoadjuvant/adjuvant treatment for stage II and III patients.
- ▶ Continuation of a treatment in the context of a clinical trial.

Low priority

- ▶ Weekly blood tests unless clinical conditions and symptoms require them.
- ▶ Radiological evaluation by considering the patient's risk/benefit ratio.

not be postponed more than 6 weeks and the intervals between cycles should not be prolonged (box 4 and box 5).

To accomplish good treatment outcomes, medical oncology services need to assure the continuum of care and guarantee punctual monitoring of potential adverse effects during the COVID-19 pandemic. To keep the safest possible conditions, telemedicine systems need to be improved.

Patient experiencing severe complications not only derived from the administration of chemotherapy but also from surgery and or radiation therapy should be considered as high priority and admitted to the hospital after triage, avoiding unnecessary visits and waiting times in the outpatient setting.

The systemic treatment of early stage colon and rectal cancer has not changed substantially over the last years. Despite the fact that only two drugs, oxaliplatin and 5-FU, are in use for the treatment of early CRC patients, some few recommendations might be highlighted in the era of the COVID-19 pandemic.

For stage II microsatellite instability—high (MSI-H) CRC patients, it has been shown that the benefit derived from a 5-FU based adjuvant treatment is limited or may be detrimental. Therefore, MSI testing should be recommended to avoid ineffective administration of therapy, potential side effects and unnecessary exposure to the risk of COVID-19. Moreover, for stage II microsatellite stable high risk and stage III colon cancer, as well as stage II and III patients with rectal cancer, the use of capecitabine instead of 5-FU should be considered as a valid option, by keeping the benefit related to the treatment but reducing the necessary appointments and the risk of COVID-19. Based on the work of Henricks *et al*,¹⁷ to avoid harmful toxicity related to the administration of capecitabine, testing for dihydropyrimidine dehydrogenase deficiency is recommended.

For low-risk stage III patients with colon cancer 3 months of adjuvant treatment, especially with the combination of capecitabine and oxaliplatin, should be considered as non-inferior to 6 months. This implies that during the COVID-19 pandemic we might rethink of the duration of the adjuvant treatment for stage III patients with colon cancer in general and use a patient risk and clinical conditions-adapted strategy to define the duration of the treatment, by taking advantage from the evidence produced by the International Duration Evaluation of Adjuvant Therapy collaboration.¹⁸

For both early-stage colon and rectal cancer treatment in the context of a clinical trial should be continued and considered as medium priority.

Weekly blood tests should be performed near to home whenever possible and the results as well as other potential side effects that might impact on the administration of the next cycle of treatment or require hospitalisation should to be communicated with telemedicine. Radiological evaluation during adjuvant treatment of both colon and rectal cancer is not generally performed. Nevertheless,

Box 6 Priorities for colon cancer: medical oncology—advanced colorectal cancer (CRC)**High priority**

- ▶ Severe complications due to the treatment (surgery, radiation, chemotherapy) that require hospitalisation. Avoid outpatient visit appointments and plan with the medical staff, after triage, admission to the ward.

Medium priority

- ▶ First-line treatment for patients with performance status (PS) 0–2 (Eastern Co-operative Oncology Group (ECOG) scale) with the goal of reducing the symptom.
- ▶ First-line treatment for patients with PS 0–2 (ECOG scale) with the goal of reducing the tumour bulk and performing curative surgery.
- ▶ First-line treatment for patients with PS 0–2 (ECOG scale) who quickly relapsed after adjuvant treatment.
- ▶ Second-line treatment for patients with PS 0–2 (ECOG scale) after short PS 1.
- ▶ Second-line treatment with immunotherapy for MSI-H mCRC patients.
- ▶ Continuation of treatment in the context of a clinical trial.

Low priority

- ▶ Delay all treatments with modest benefit expected, maintenance therapy and treatments in patients with low disease burden and slow progression.
- ▶ Delay all treatment including first line for patients with PS 3 and heavy comorbidities.
- ▶ Delay all treatments for those patients who had severe complications also during the adjuvant therapy.
- ▶ Delay all treatment for symptomatic slowly growing recurrent disease.

for patients with suspected symptoms of early relapse, radiological assessments should be performed in short time by considering that the risk of progression of disease and delay of potential curative treatment might be higher than the risk of COVID-19.

For stage II and III patients with rectal cancer, radiological assessment meant to evaluate the response to treatment and define the next step of treatment, should not be delayed.

Finally, even if the drugs used for the adjuvant and neoadjuvant treatment of CRC do not commonly induce neutropenia and febrile neutropenia, patients should be monitored for such complications.

Priorities for metastatic CRC

High priority should be considered for those patients with treatment-related complications and for patients experiencing cancer-related treatment organ dysfunctions, namely patients in visceral crisis (**box 6**). For all the cases who do not represent a medical emergency, the priority should be defined based on the impact that the treatment will have on the QOL of the patients (reduction of cancer related-symptoms and or complications) and on survival.

In particular, patients in good clinical condition, for which the start of a first-line treatment can reduce the tumour bulk and lead to a radical curative surgery or reduce cancer-related symptoms or complications (such

as pain, dyspnoea, kidney failure due to compression) are considered as medium priority. Therefore, the treatment should start within 6 weeks from the diagnosis. Same is true for patients who rapidly relapsed either quickly after adjuvant treatment, patients who did not benefit from first-line treatment (eg, with a short PS1)) and those with MSI-H tumours that could benefit from immunotherapy. The kind of treatment needs to be defined according to the biology of the tumour as it is recommended in the national and international guidelines for the treatment of metastatic CRC (mCRC). In particular, decision from a multidisciplinary team should be applied.

Treatment should be applied in the outpatient setting whenever the clinical conditions permit it. Capecitabine can replace the use of 5-FU. Cetuximab should be considered for a 2-week administration rather weekly administration. Alternatively, panitumumab can be prescribed. For patients at risk of neutropenia and febrile neutropenia, the use of granulocyte growth factors may be considered.

Patients whose treatment in the metastatic setting has a limited effect on survival, patients whose tumours progress slowly or patients under maintenance treatment are considered as low priority. For those patients a 3-weekly administration could be considered without affecting the progression of the disease. Finally, for those patients under third or fourth-line treatment with regorafenib or Tas-102, telemedicine weekly controls for side effects and drug dose adjustment are recommended. Blood tests for both medium and high priority patients should be performed near home and communicated by using telemedicine. For patients with bone metastasis who require the administration of intravenous bisphosphonates, treatment should be administered with a long interval, for examples each 3 months. Finally, for molecularly defined poor prognosis patients (v-Raf murine sarcoma viral oncogene homolog B V600E (BRAFV600E), rat sarcoma virus mutated) the continuation of a treatment in the frame of clinical trials is recommended.

Priorities for CRC radiation oncology

Apart from rectal cancer, where radiotherapy alone or in combination with chemotherapy represents the gold standard of treatment in the early setting, the indications for radiation therapy in CRC are limited. Immediate radiation therapy should be initiated in patients with acute spinal cord compression, symptomatic brain metastases not improving with steroidal medication and any urgent irradiation with an expected impact on survival or a modifying effect on the risk of disabling sequelae and/or QOL, such as compression with organ failure, pain, bleeding, fractures (**box 7**). The optimisation of locoregional control and the improvement of survival define the priority of the interventions in radiation therapy as both neoadjuvant and adjuvant treatment of stage II and III rectal cancer are considered as medium priority. Same is true for those patients with oligometastatic disease for whom curative surgery or a systemic treatment might not be applied. In those cases selective internal

Box 7 Priorities for colorectal cancer (CRC): radiation oncology

High priority

- ▶ Severe complications due to the disease progression (compression with organ failure, bleeding, pain, fractures, mediastinal mass with symptoms of compression, symptomatic brain metastases). Avoid outpatient visit appointments and plan with the medical staff, after triage, admission to the ward.

Medium priority

- ▶ Neoadjuvant/adjuvant treatment for stage II/III rectal cancer.
- ▶ Selective internal radiation therapy for patients with oligometastatic disease for which systemic treatment is contraindicated.

Low priority

- ▶ Delay all treatments with modest benefit expected, for symptomatic slowly growing recurrent disease and for patients with low disease burden and slow progression.

radiation therapy on liver metastasis or stereotactic radiation therapy of single lung metastasis should be considered as medium priority, thus not delayed.

Moreover, to reduce the admissions to the institutions without harming the effect of radiation therapy, short course radiotherapy (5×5)±capecitabine instead of long course radiotherapy should be preferred if clinically indicated. Finally, all cases in which radiation therapy might give a modest benefit, such as for symptomatic slowly growing recurrent disease and for patients with low disease burden and slow progression, are considered as low priority.

CONCLUSIONS

COVID-19 has posed an unprecedented challenge to healthcare systems. Since patients with cancer are at higher risk of developing the disease and its complications, the current pandemic has also challenged oncologists. In very short time, oncologists have needed to reorganise cancer care in order to dramatically reduce hospital visits, admissions and therapy-induced immune-related complications but without compromising cancer outcomes. Without robust scientific evidence, oncologists have needed to redefined priorities for the management of cancer treatment in the COVID-19 era. All the impactful decisions made and published based on expert opinions are not meant to substitute the current clinical guidelines. In that respect, we, with the current work, as well as other collaborators and experts in the field, have tried to summarise practical recommendations for cancer treatment management during COVID-19.

The degree of spread of COVID-19 is different across countries, as the way how countries are reacting to the pandemic due to economic, political as well as healthcare system differences vary. Indeed, WHO has defined different response plans, according to the disease spread in single countries. Those differences should also inform the prioritisation of interventions in oncology. A very good example of how European cancer centres have

organised their healthcare systems at an unprecedented scale has been recently reported by van de Haar *et al.*¹⁹

Therefore, the current recommendations for CRC management during the COVID era need to be interpreted and adapted within the national and regional dispositions based on the ability of the own health system to reorganise and reshape existing models.

Moreover, the above summarised clinical guidance for CRC management is intended to suggest and not substitute local, national and international guidelines and guide the development of action plans to maintain a quality cancer service. Useful information can be found at <https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/breast-cancer-in-the-covid-19-era>

Finally, several other societies have issued some guidance for cancer care as well as for the management of clinical trials during the COVID-19 pandemic. In particular, further guidance for CRC can be found at

- ▶ <https://www.facs.org/covid-19/clinical-guidance/elective-case/colorectal-cancer>
- ▶ <https://www.essoweb.org/news/esso-statement-covid-19/>
- ▶ <https://www.asco.org/asco-coronavirus-information>
- ▶ <https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information>
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- ▶ https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

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ORCID iDs

Loredana Vecchione <http://orcid.org/0000-0003-3942-5498>

Sebastian Stintzing <http://orcid.org/0000-0002-3297-5801>

Florian Lordick <http://orcid.org/0000-0001-8591-9339>

REFERENCES

- Zhu N, Zhang D, Wang W, *et al.* A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med Overseas Ed* 2020;382:727–33.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA* 2020;323:1239.
- WHO. Coronavirus disease (COVID-19) Situation Report– 106, 5th of May [Internet]. Available: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200505covid-19-sitrep-106.pdf?sfvrsn=47090f63_2
- Emanuel EJ, Persad G, Upshur R, *et al.* Fair allocation of scarce medical resources in the time of Covid-19. *N Engl J Med* 2020. doi:10.1056/NEJMs2005114
- Kamboj M, Sepkowitz KA. Nosocomial infections in patients with cancer. *Lancet Oncol* 2009;10:589–97.
- Li J-Y, Duan X-F, Wang L-P, *et al.* Selective depletion of regulatory T cell subsets by docetaxel treatment in patients with nonsmall cell lung cancer. *J Immunol Res* 2014;2014:1–10.
- Longbottom ER, Torrance HDT, Owen HC, *et al.* Features of postoperative immune suppression are reversible with interferon gamma and independent of interleukin-6 pathways. *Ann Surg* 2016;264:370–7.
- Sica A, Massarotti M. Myeloid suppressor cells in cancer and autoimmunity. *J Autoimmun* 2017;85:117–25.
- Alemanno A. The precautionary principle. *Handb EEA Law* 2015:839–51.
- WHO. COVID-19: operational guidance for maintaining essential health services during an outbreak interim guidance. Available: <https://apps.who.int/iris/handle/10665/331561>
- Problems IP. *Step four: identify priority problems and goals to improve the model of care*, 2019: 105–20.
- Cherny NI, Dafni U, Bogaerts J, *et al.* ESMO-Magnitude of clinical benefit scale version 1.1. *Ann Oncol* 2017;28:2340–66.
- Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: understanding and stepping-up action on the financial toxicity of cancer treatment. *CA Cancer J Clin* 2018;68:153–65.
- Kesson EM, Allardice GM, George WD, *et al.* Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. *BMJ* 2012;344:e2718.
- Chalabi M, Fanchi LF, Dijkstra KK, *et al.* Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med* 2020;26:566–76.
- Seymour MT, Morton D, on behalf of the International FOxTROT Trial Investigators. FOxTROT: an international randomised controlled trial in 1052 patients (PTS) evaluating neoadjuvant chemotherapy (NAc) for colon cancer. *JCO* 2019;37:3504.
- Henricks LM, Lunenburg CATC, de Man FM, *et al.* Dpyd genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol* 2018;19:1459–67.
- Grothey A, Sobrero AF, Shields AF, *et al.* Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med* 2018;378:1177–88.
- van de Haar J, Hoes LR, Coles CE, *et al.* Caring for patients with cancer in the COVID-19 era. *Nat Med* 2020;26:665–71.