

## Principles for Management of Colorectal Cancer Patients During the COVID-19 Pandemic

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Every decision and recommendation we make as oncologists involves an analysis of the risk-to-benefit ratio for each specific patient. In the current pandemic, although the benefits of cancer therapies remain the same, the risks have increased substantially, warranting careful reconsideration of many of our practices. The risk-to-benefit ratio now needs to be reconsidered for individual patients based on their disease status, age, frailty, and comorbidities.

Each city and each hospital or hospital system will have a different prevalence of COVID-19, with differing ability to accomplish social distancing. Timing of a surge of cases, and limitations on the availability of health care staff and facilities will need to be considered when forming treatment decisions for individual patients. To that end, the COVID-19 Working Group of the NCCN Colon, Rectal, and Anal Cancers Guidelines Panel recommends strong consideration of the following modifications to standard treatment guidelines during this pandemic:

- 1) Social distancing mandates that every in-person interaction between the patient and the health care system be scrutinized and only truly essential physical contacts between the patient and the health care system occur, with all others being reduced or delayed until resolution of the pandemic in your area. To that effect, minimize blood tests, scans, prescriptions, and routine tests to diminish risk of viral exposure to the patient and diminish the burden on over-extended medical staff. Telephone and telemedicine visits should replace routine face-to-face clinic visits for nearly all patients.
- 2) The COVID-19 Working Group of the NCCN Colon, Rectal, and Anal Cancers Guidelines Panel endorses the surgical recommendations from the [Society of Surgical Oncologists for Colorectal Cancer](#).
- 3) Oral therapies that may allow treatment at home should be favored when clinically appropriate. Also favor oral and other regimens that spare the need for placement of a vascular access device, as this procedure would incur risk of COVID-19 exposure.
- 4) For patients in whom single-agent capecitabine is a reasonable consideration, consider management without routine labs in the absence of symptoms requiring investigation. This would permit treatment at home without extra exposure.
- 5) The alternative capecitabine dosing schedule of 1000 mg/m<sup>2</sup> twice daily orally, days 1–7 and 15–21 of a 28-day cycle, can reduce toxicity and need for intensive monitoring.

- 6) For adjuvant therapy, extra emphasis during this pandemic should be placed on the incremental benefit of any therapy you are initiating and the anticipated survival benefit for each patient, versus the risks of exposure to the virus, bearing in mind the individual's comorbidities and degree of frailty, as well as caregivers and family members at home. In most stage III colon cases, 3 months of capecitabine/oxaliplatin (CapeOx) would be a preferred regimen, given the data from the IDEA trial and the incremental risk of further exposure beyond 3 months. Even for high-risk stage III patients, the incremental benefit of 6 months of adjuvant therapy must be weighed against the risk of frequent face-to-face encounters. For patients unable to receive CapeOx, clinicians should consider leucovorin/5-fluorouracil (5-FU)/oxaliplatin (FOLFOX) without bolus 5-FU.
- 7) For patients with newly diagnosed stage 2–3 colon cancer who are unable to have surgery due to COVID-19 constraints on operating room availability, consider a course of neoadjuvant capecitabine or CapeOx chemotherapy to bridge time to surgery.
- 8) Strongly consider using only short-course pelvic RT during this pandemic. Treatment in 5 fractions instead of 28 dramatically decreases the patient's exposures and risks of contracting the virus, and as resources become constrained due to technicians and other staff becoming ill, many more patients can be accommodated if the 5-treatment approach is used. Further, consider the risk of interruption if a patient on a long course were to contract coronavirus after only a portion of the 28 planned treatments were given. Recent evidence indicates that it is safe, with improved tumor downstaging, to delay resection of rectal cancer after short-course radiation by 6–8 weeks or longer to prevent the need for an operation during COVID-19 surge times.
- 9) Strongly consider several months delay of routine surveillance scans and carcinoembryonic antigen (CEA) monitoring until the pandemic has resolved in your area. Use telephone or telemedicine visits to evaluate patient and assure clinical stability.
- 10) Strongly consider delay of surveillance colonoscopies until the risk of coronavirus exposure resolves.
- 11) For metastatic disease, consider single-agent capecitabine when at all reasonable, and consider CapeOx on a 21-day cycle over other 14-day cycle regimens, to reduce contact of the patient with the clinic and chemotherapy unit. Given the added risks of toxicity, leucovorin/fluorouracil/oxaliplatin/irinotecan (FOLFOXIRI) use during this epidemic should only be used in extenuating circumstances.
- 12) Consider empiric dose reductions for patients with comorbidities that increase the risk of COVID-19 complications or for patients whose social situations prevent adequate social distancing.

- 13) Strongly consider dose reductions over use of pegfilgrastim to avoid extra trips for pegfilgrastim administration (unless a take-home self-administered option exists).
- 14) Consider longer treatment intervals as is consistent with drug kinetics. (eg, less frequent administration of checkpoint inhibitors). Target engagement data suggest that efficacy can be expected to be maintained with the dose at twice the interval (eg, nivolumab 480 mg every 8 weeks or pembrolizumab 400 mg IV every 6 weeks<sup>a</sup>).
- 15) Consider upfront anti-PD1 therapy for metastatic MMR-deficient (dMMR)/microsatellite instability-high (MSI-H) cancers instead of cytotoxic chemotherapy.
- 16) For maintenance therapy, consider giving capecitabine without a parenteral biologic agent (eg, de-escalating FOLFOX + bevacizumab to capecitabine monotherapy).
- 17) In patients with unresectable metastatic disease, consider treatment holidays of as long as 12 weeks as appropriate.
- 18) In patients with metastatic disease and abnormal CEA, check CEA at times that scans would be considered (draw at chemotherapy visit to avoid an extra contact and extra travel). Unequivocal substantial change in CEA one way or the other may suffice as adequate information for clinical decision-making.
- 19) The frequency of visits for central venous access catheter flushes should be extended to at least 12 weeks given the low level of evidence to do these more frequently. For patients not on active therapy, the risk of exposure to coronavirus may outweigh the benefit of a maintenance port flush.
- 20) Consider switching to targeted therapies, without concurrent use of cytotoxic agents, for those patients whose cancers need treatment and are refractory to 5-FU/capecitabine as a single agent and possess either *HER2* amplification, *BRAF* V600 mutations, or *RAS/RAF* wild-type cancers.
- 21) Weekly cetuximab should not be given. Regimens with every-other-week anti-epidermal growth factor receptor (EGFR) dosing should be prioritized as opposed to weekly dosing, including for *BRAF*-mutant cancers undergoing *BRAF* tyrosine kinase inhibitor (TKI) + anti-EGFR mAb therapy.
- 22) Consider biopsies only when absolutely needed for clinical decision-making that cannot wait until the end of expected peak of the pandemic. Consider oncologic benefit of biopsy versus possible risk of infection and possible exposure to coronavirus. Consider whether observation and repeat imaging in 12 weeks may be a good alternative to an

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<sup>a</sup>The NCCN Colon/Rectal/Anal/Small Bowel Panel agrees with the pembrolizumab recommendation as included in the NCCN Melanoma Panel recommendation which says: "This regimen is not FDA-approved at present. However, NCCN, ECOG-ACRIN, and SWOG melanoma leadership have reviewed the pharmacokinetic data, and in light of COVID-19 strongly support the use of this regimen based on the following publicly available evidence for pembrolizumab 400 mg flat dose every 6 weeks."

invasive procedure now, especially if the COVID-19 epidemic will limit availability or safety of therapeutic intervention now.

- 23) Consider postponing local or locoregional therapies (intra-arterial chemotherapy/ metastasectomy/ablation/intra-arterial therapy/ radiotherapy) until the risk of coronavirus infection diminishes.
- 24) Consider postponing enrollment to clinical trials that require sequential biopsies or other interventions or frequent hospital visits until resolution of the COVID-19 risk.
- 25) GOALS OF CARE: We recognize it's a challenging time to have these difficult discussions, but all patients with metastatic disease, especially older adults and those with high comorbidities, should have goals of care and do not resuscitate (DNR) discussions as clinically appropriate. Social distancing will likely require that many of these discussions will need to happen by phone or telemedicine. Clinicians should be aware that patients with cancer who require ventilation for COVID-19 have a dismal prognosis.