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Modifying Practices in GI Oncology in the Face of COVID19: Recommendations from Expert Oncologists on Minimizing Patient Risk

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Introduction:

The COVID19 pandemic has spread rapidly across the world, causing significant disruption to the healthcare system as a whole. This disruption has presented new and unprecedented challenges in the care of cancer patients with both curable and non-curable forms of cancer. Providers have been forced to carefully reexamine the necessity and risk vs. benefit ratios of even the most common and routine procedures and treatments in light of the need for physical distancing to ‘flatten the curve’ of infection rates, and also to mitigate the risk of infection in our vulnerable patient population.

In this context, a group of expert oncologists in the field of gastrointestinal (GI) oncology recently discussed and compiled recommendations for new practices as we all adapt to the quickly-changing landscape. The discussion focused on balancing logistics of care with the need to practice physical distancing to mitigate exposure of this cancer patient population to further increased risks, and managing each situation on a case-by-case basis with special consideration toward differentiating between patients at high risk vs. relatively lower risk of COVID19 infection in the community, as well as intent of treatment (intent-to-cure vs. palliative-intent). As of April 1, 2020, 10 of these oncologists had reported that their centers had adopted institution-wide guidelines with some degree of formality; others also cited interpretation of the American Society of Clinical Oncology (ASCO) statement on general care of patients with cancer during the COVID19 pandemic, posted online March 13, 2020; much of the practice points offered for consideration via ASCO and other professional societies are predicated on direction from the Center for Disease Control (CDC) to curtail elective surgeries and other non-urgent medical interventions in general. Some cancer centers have created acute care clinics designed to focus on cancer-related complications, such as adverse events from chemotherapy, in an effort to minimize further burden on already overtaxed emergency room and inpatient hospital settings, and to also minimize exposure of our cancer patients to potential COVID19 infection. As the risks of cancer progression are particularly high for most cases of gastrointestinal cancers, the need to carefully weigh risks vs. benefits is critical. What is clear is the risk to benefit ratio has changed
dramatically due to the risks imposed by the COVID19 virus, including inducing clinically emergent forms of morbidity as well as potentially increased risk of death in the cancer population.

**Most commonly offered tips for modifying treatment and practice in this population included:**

1. As a more general approach to patient care, regardless of tumor type, many cancer centers across the country have shifted to telemedicine approaches to patient visits, to preserve physical distancing and minimizing patient interactions with potential infected persons both inside and outside of the oncology clinic setting.

2. Discontinuation of 5-FU bolus/leucovorin combinations for infusional combination regimens that utilize 5-FU infusions as backbones of therapy (i.e. FOLFOX, FOLFIRI, FOLFIRINOX), most especially when given with palliative intent. Additionally, in the case of the FOLFIRINOX regimen in particular, with a >50% rate of neutropenia, consideration of avoiding this specific combination altogether at the current time in favor of modified dosing and/or number of combination drugs.

3. Consideration for delaying or not proceeding with risk-reducing adjuvant chemotherapy for patients with resected high-risk stage II colon carcinomas; and the same for patients at high risk of COVID19 infection with resected stage III colon carcinomas, vs. shortening duration (3 months vs. 6 months) and/or instituting oral chemotherapy (capecitabine in place of bolus/infusional 5-FU-based regimens) as alternate tactics for adjuvant treatment approaches.

4. For cases of localized rectal cancer, shortening the duration of radiation treatment using the “short-course RT” approach favored in Europe.

5. Assessment of timing of routine surveillance imaging scans for patients with history of treated GI malignancy and low risk of recurrence, most especially in context of scarcity of personal protective equipment that would be required by patient and/or imaging teams.
6. Case-by-case discussion with patients with metastatic incurable forms of GI malignancies currently on treatment and with stable disease and/or minimal tumor burden, with consideration of risks vs. benefits of treatment as compared to risk of acquiring and suffering from morbidity and related sequelae of COVID19 infection.

7. For patients with metastatic, borderline resectable, or locally advanced pancreatic cancer undergoing treatment with chemotherapy with gemcitabine with nab-paclitaxel (whether for palliative or neoadjuvant intent), deleting day 8 of the standard regimen, providing infusions of both drugs on days 1 and 15 of each 28-day cycle, to avoid expected nadirs during that middle week. At least one previously published study supports that this approach improves patient tolerance of this chemotherapeutic combination without significantly compromising efficacy.

8. Regarding empiric use of growth factor supplementation for chemotherapy regimens with high potential for inducing neutropenia, guidance from ASCO suggesting that continued use of prophylactic growth factors may be warranted. Further discussion among our experts delved into the ideal situation of avoiding additional clinic visits in this scenario, for example though use of take-home versions of the growth factor support injections (i.e., pegfilgrastim body injector), and also considering reduction of chemotherapy doses in an effort to further avoid neutropenia from occurring.

9. Switching to and modification of dosing, scheduling of administration and of monitoring, and overall implementation of oral chemotherapeutic or biologic agents when feasible, in an effort to both reduce cytopenias and also minimize the need for in-person clinical evaluation and exposure to potential infected individuals. Examples included less frequent evaluation of patients on Regorafenib (e.g. every two weeks rather than weekly for the first cycle), alternate-week dosing of trifluridine-tipiracil (TAS-102) (7 days on/7 days off), and implementation of Capecitabine in place of bolus/infusional 5-FU for treatment of anal carcinoma and adjuvant or metastatic colorectal carcinomas.
The table included below categorizes these and other suggested modifications by condition, risk of COVID19 infection, and by GI organ/disease site.

GI oncology treatment modification proposal (created with input from GI oncologists at Duke Cancer Institute, University of Minnesota, MD Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, Fred Hutchinson Cancer Center, University of Wisconsin, University of Texas-Southwestern, Vanderbilt-Ingram Cancer Center, University of California-San Francisco, and the Cleveland Clinic)

Table 1. Most commonly discussed proposed modifications to logistics of care.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Propositions</th>
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<tbody>
<tr>
<td><strong>Patients actively receiving treatment</strong></td>
<td></td>
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<tr>
<td>Low risk chemotherapy (single or doublet +/- biologic)</td>
<td>Utilize phone or telemmedicine visits where possible to avoid additional exposure of patients to potential COVID19 infection.</td>
</tr>
<tr>
<td>High risk chemotherapy (triplet cytotoxic chemotherapy +/- biologic)</td>
<td>• Decrease intensity of chemotherapy to doublets when possible (example: instead of FOLFIRINOX or FOLFOXIRI, consider FOLFOX or FOLFIRI instead).</td>
</tr>
<tr>
<td></td>
<td>• Lower threshold for dose reductions.</td>
</tr>
<tr>
<td>Heavily pretreated patients.</td>
<td>Re-evaluate risk/benefit of continuing treatment and discuss goals of care.</td>
</tr>
<tr>
<td>Oral chemotherapy</td>
<td>Transition to telehealth in place of in-person evaluation.</td>
</tr>
<tr>
<td>Prominent example in GI Oncology: 5-FU based regimens</td>
<td>Discontinue 5-FU infusions in favor of changing to oral capecitabine (Xeloda) when possible. Otherwise, if continuing infusional 5-FU, then omit 5-FU bolus.</td>
</tr>
<tr>
<td><strong>Patients not actively receiving treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Surveillance</td>
<td>• Postpone all routine surveillance visits; convert to telehealth as needed</td>
</tr>
<tr>
<td></td>
<td>• Delay restaging scans in patients with metastatic cancer who are otherwise doing well</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>Labs</td>
<td>• Obtain labs closer to home whenever possible, especially if results are visible in patient portals in the electronic medical records (e.g. Care Everywhere or equivalent function).</td>
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- Reduce frequency of lab draws to every other cycle or less based on stability and symptoms.

### Table 2. Proposed modifications stratified by COVID19-related risk of infection

<table>
<thead>
<tr>
<th>Risk considerations</th>
<th>Propositions</th>
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<tbody>
<tr>
<td>Patients at high risk of COVID19 infection</td>
<td>As defined by age, comorbidities including but not limited to cardiovascular disease and pulmonary disease; patients with diabetes, active smokers, and/or residing in nursing facilities or group homes. Discuss risk/benefit of therapy, in light of evidence that cancer patients are at potentially greater risk of infection compared to community (Yu et al, JAMA Onc 2020). Lean toward delaying immunosuppressive therapy until community risk decreases.</td>
</tr>
<tr>
<td>Patients at community risk of Covid-19 infection.</td>
<td>Although active cancer patients likely have higher than community risk, this category includes patients without high-risk factors as detailed above. Proceed with treatment on case-by-case basis after discussion of risks and incorporating patient preferences and values. Lean toward continuing immunosuppressive cancer-directed therapy but institute measures to ameliorate risk of immunosuppression</td>
</tr>
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</table>

### Table 3. Proposed modifications and accommodations to treatment listed by disease-specific/organ site.

<table>
<thead>
<tr>
<th>Organs</th>
<th>Oncological situations</th>
<th>Propositions</th>
</tr>
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</table>
| Pancreas    | Unresectable (includes locally advanced cases as well as those with distant metastatic disease) | • Avoid FOLFIRINOX due to inherently high risk of neutropenia; consider doublet-regimens instead (e.g. FOLFOX; otherwise gemcitabine with nab-paclitaxel, if not otherwise refractory)  
• If necessary, use growth factor and dose reduce  
• Use every-other-week gemcitabine/nab-paclitaxel.                                                                                                                                                                                                 |
| Rectum (localized) | Chemoradiation/radiation completed or ongoing                                       | • Delay the surgical intervention up to 12 weeks on observation (GRECCAR 6 showed that there is no difference in pathologic complete response with a delay of 11 or 7 weeks)  
• If the delay is beyond 12 weeks, consider restaging and guiding therapy on the basis of treatment response.                                                                                                                                                             |
| Preoperative radiation is required | - Minimize use of neoadjuvant chemotherapy for average risk patients.
- Prefer short course RT (5x5) and surgery at 12 weeks |
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<tbody>
<tr>
<td>Particular high-risk cases T4 or N2</td>
<td>Proceed with neoadjuvant chemotherapy with preference for CAPOX over FOLFOX, followed by SBRT.</td>
</tr>
<tr>
<td>Major response to chemoradiation</td>
<td>Discuss surgical resection, and consider watch-and-wait strategy with frequent follow-up surveillance</td>
</tr>
<tr>
<td>Colon (localized)</td>
<td>Localized cancer &lt;T4 (symptomatic and non-symptomatic)</td>
</tr>
<tr>
<td>Particular cases T4</td>
<td>Proceed with or delay surgical resection; some suggested consideration of neoadjuvant chemotherapy with preference for CAPOX and surgery after the COVID19 pandemic</td>
</tr>
<tr>
<td>Patients at high risk of COVID19 complications</td>
<td>Delay of surgery for between 4 to 6 weeks to be discussed according to the benefit-risk ratio</td>
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</tbody>
</table>
| Adjuvant chemotherapy indicated | Stage III and stage II (high risk) | - Prefer CapOx (3 or 6 months) instead of FOLFOX adjuvant therapy.
- For new onset or ongoing adjuvant therapy, consider stopping early (3 months) or switching to capecitabine or 5FU alone for remainder.
- Re-assess risk/benefit in stage II colon cancer.
- In patients already on FOLFOX, preference for dropping 5FU bolus and leucovorin.
- Consider early discontinuation of oxaliplatin. If on 5-FU alone, consider switch to capecitabine
- For patients at low risk, discuss the myelosuppression of oxaliplatin and the use of capecitabine monotherapy
- For patients at high risk of COVID19 complications or with anticipated low absolute risk reduction with adjuvant chemotherapy, discuss not administering chemotherapy |
| Metastatic colorectal cancer (1st and 2nd lines) | Resectable or potentially resectable metastatic disease | - Virtual consultation with liver surgery at baseline and after neoadjuvant chemotherapy is encouraged
- For resectable patients, delay surgery until after the COVID19 pandemic, with or without preoperative chemotherapy according to neoplastic characteristics. |
<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
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| Non-resectable, multiorgan metastatic disease                           | • Chemotherapy: monotherapy (preferably capecitabine) or CAPOX with or without targeted therapies; avoid FOLFOXIRI  
  • For patients with metastatic cancer and stable/minimal disease, consider a treatment break  
  • Chemotherapy breaks in lieu of maintenance are preferable.  
  • If maintenance therapy is desired, capecitabine alone or with bevacizumab  
  • If patients are 5-FU refractory, irinotecan with or without biologics (either bevacizumab or a EGFR inhibitor) would be preferred over FOLFIRI |
| Metastatic colorectal cancer (beyond 2nd-line treatment)                | Non-resectable, non-trial (note: many centers have halted new enrollments onto therapeutic clinical trials due to the pandemic)  
  • Up-front goals of care discussion are warranted  
  • Use Regorafenib and Trifluridine-Tipiracil (TAS-102) with prudence, given the low efficacy and potential toxicities.  
  • Regorafenib is preferred over TAS-102 due to the risk of leucopenia and neutropenia.  
  • For TAS-102, alternate 1 week on/1 week off to reduce risk of myelosuppression.  
  • Discuss a therapeutic pause in cases of stable disease. |
| Metastatic colorectal cancer (MSI-H on immunotherapy)                   | Double time between infusions (eg, from q3week pembrolizumab to q6week)  
  • For PD-1/PD-L1 inhibitor duration of therapy >12 months, preference for holding immunotherapy |
| Localized anal cancer                                                   | Consider oral Capecitabine instead of infusional 5-FU, concurrent with standard radiation course; if using 5-FU or Capecitabine in combination with mitomycin, consider holding mitomycin for scheduled cycle 2 (Day 29 of overall treatment). |
| Well-differentiated low-grade neuroendocrine tumors.                   | Consider holding octreotide/lanreotide in absence of carcinoid syndrome symptoms to avoid clinic visits. |
| Upper GI malignancies (esophageal, gastroesophageal junction, gastric) | Metastatic and PDL-1 expression levels that meet criteria for checkpoint immunotherapy  
  • Double time between infusions (eg, from q3week pembrolizumab to q6week)  
  • For PD-1/PD-L1 inhibitor duration of therapy >12 months, preference for holding immunotherapy |