Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Changing Oncology Treatment Paradigms in the COVID-19 Pandemic

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The COVID-19 pandemic has forced the oncology community to quickly reassess and adapt standard-of-care practices in an effort to minimize risk of COVID-specific infection-related morbidity in cancer patients. Newly released analysis confirms deep concerns that patients with cancer undergoing active treatment, and/or with intact metastatic disease,[1] are among the most particularly vulnerable patients amidst this pandemic. Physicians and care teams helping patients with cancer have had to make or at least consider difficult decisions, including how to best balance the risk-safety profile of cancer treatment with emerging and rapidly evolving risks associated with COVID-19 infection and the broad range of potential sequelae of this infection. This overarching concern is especially present for patients with gastrointestinal (GI) cancers, which represent a particularly broad set of diverse disease entities that require multispeciality input and management. Along with the significant delays in cancer treatment, colorectal cancer (CRC) screening has also dropped down to 86% to 94%.[2]

Alarming data are emerging to support the hypothesis that the severity of COVID-19 increases in the elderly population and in patients with comorbidity. CRC generally affects people older than 60 years, and COVID-19 further increases the risk for patients with CRC, and patients with GI cancer in general, due to the immunosuppressive treatments they receive. Our institution was 1 of 10 cancer centers that recently published potential modifications that could be incorporated to help maximize safety for patients with GI cancers during this challenging time.[3] Other experts from areas of Europe hit most hard with COVID-19 have also published timely suggestions on management from the surgical oncology and operative risk aspect for patients with CRC.[4-6] The presentation of center-based experiences for areas hit earliest and hardest by COVID-19 have confirmed that patients with GI cancer are at relatively high risk, especially with the high proportion of patients with metastatic/stage IV forms of cancer that usually would require ongoing treatment with palliative-intent chemotherapy. During the 2020 Virtual Meeting of the American Association for Cancer Research (AACR) April 28, Dai et al.[1] reported the first large-cohort multicenter study on impact of COVID-19 on patients with cancer, with confirmation that patients with cancer as a whole are more vulnerable to the virus. Of the total cohort of COVID-19-infected patients with cancer, 19 (~18%) of 105 had GI cancer (type not specified) or esophagus cancer. The percentage of COVID-19 in patients with cancer, specifically with GI cancers at the Gustave Roussy Institute in Paris, also presented at the AACR meeting, was 15.1%. The study from China from Dai et al.[1] reported that the intensive care unit (ICU) admission rate for this population was 19% to 23%, with 30% to 35% having critical symptoms. Although the overall times to ICU admission and mechanical ventilation were not as short as in the lung cancer population, nonetheless these statistics should sound the alarm to reexamine how our patients with GI cancer can best be treated as safely as possible during this ongoing pandemic. This point is especially crucial considering the many unknowns we face as a society in the months (and perhaps years) to come, including impact on health care of patients with cancer with anticipated second and third waves of infection, and beyond.

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With these significant risk and potential treatment delays, managing anxiety in patients with CRC is critical during the COVID-19 pandemic. There are numerous practical adaptations and modifications for treating patients with GI cancer safely from a logistical point of view, expanded on elsewhere,[3] that can help ease patient concerns. Transitioning patients to oral chemotherapeutic drugs in an effort to minimize in-clinic exposure to COVID-19 infection is just one specific example that can be easily implemented; however, from a broader and more strategic standpoint, now is the time to wholly reassess some strategies in this patient population, for standard-of-care but most especially for rational clinical trial design. We are and will continue to be forced to make this reassessment from every angle, including feasibility to avoid worsening already concerning extent of financial toxicity to patients, avoiding overburdening surgical staff due to a backlog of delayed surgeries, and ongoing concerns about availability of protective personal equipment (PPE), among many issues.

For example, a specific patient subset that merits careful attention is the cohort of patients with localized and potentially resectable forms of cancer that were diagnosed just before or during the pandemic. Under normal circumstances, such patients would routinely be scheduled for surgical resections as part of an intent-to-cure strategy for treatment; this is the case for multiple types of cancers, including early- to mid-stage forms of CRCs, which have not to date met standards for the label of "immunogenic" or otherwise "hot" tumor targets for immunotherapy. However, the rapid expansion of the current crisis has not only forced cancellation of elective surgeries, but also made the need to assess risk/benefit ratio of proceeding with surgery during the pandemic versus trying alternate strategies (eg, chemotherapy before surgery) to delay surgery and thus minimize intra- and perioperative risk of COVID-19 infection.

Let us use the concept of neoadjuvant/upfront chemotherapy approaches, such as that used in the FOxTROT trial, as an example whose intent may be repurposed in the current setting. This trial, with results reported at the American Society of Clinical Oncology Annual Meeting in 2019,[7] was an attempt to examine the potential utility of 6 weeks of upfront/neoadjuvant-intent FOLFOX chemotherapy treatment for patients with nonmetastatic resectable colon cancer in patients with advanced T stage (T3-T4), clinical N0-N2, and M0 disease before surgical resection. Although there was no significant improvement in overall survival compared with upfront surgery, the report of histological regression in 59% of patients who received neoadjuvant chemotherapy opened the door to consideration of alternative strategies and tactics, including sequence and timing of administration of standard as well as novel treatment modalities. [Note: the authors of this editorial were not involved in the design, administration, or any other aspect of this trial; we are citing the strategy as an example but not promoting its widespread use without further analysis.] Although neoadjuvant chemotherapy may not be a current standard of care for resectable colon cancer, considering this approach for elderly patients, for example, and/or patients with other significant morbid conditions might confer potential benefit by postponing current risks of surgical intervention and potentially alleviate the congestion of operating room schedules that many centers are facing and probably will face in the coming months. At least 1 group has published considerations of a similar strategy for patients with colonic (nonrectal) cancers.[5] Cancer-directed benefits would include potential for suppressing tumor growth while viably delaying surgery, and reducing the burden of micrometastasis, a rationale that is the same for the growing adoption of this strategy for resectable pancreatic cancers[8] and with rectal cancer using the "total neoadjuvant therapy" approach.[9,10] On the flip side, veering from the established standard of care also harbors risks, including progression of higher-stage tumors that were resectable at time of diagnosis, and a neoadjuvant approach could be detrimental to any patients with near-obstructive or bleeding tumors at risk for colon perforation. Another drawback of the FOxTROT approach would be uncertain value without full lymph node sampling; the risk would be overtreating patients who ultimately were found to be "downstaged" to stage I or II colon carcinoma, leaving uncertainty as to whether their cancer had already been at that stage, with negative nodal status, at the time of diagnosis. It would further be more challenging to adequately assess response to therapy, unless it were done via endoscopy to complement radiologic assessment, and biomarker assessment of carcinoembryonic antigen, which may not be of much utility in half of patients who have normal baseline values at diagnosis.[11] The trial investigators noted that, although initial analysis was performed of the study population unselected for KRAS-status, there was an improvement of the hazard ratio when excluding patients with mismatch repair deficiency; the investigators' conclusion was that the neoadjuvant approach proposed by FOxTROT would be of most utility in patients with tumors without mismatch repair deficiency.[7] The trial is not yet published in its entirety, so some questions remain about the validity of this approach in larger cohorts and also among evolving changes in molecular targeted approaches for nonmetastatic forms of colon cancer currently under investigation in other trials. Meanwhile, trials examining first-line treatment of patients with metastatic CRCs with deficient mismatch repair may provide further insight; such trials were scheduled to be presented at the 2020 Annual Meeting of the American Society of Clinical Oncology, and are now expected to be presented May 29 to 31, 2020, in the form of a virtual meeting. If positive for significant response rate, that treatment strategy (checkpoint immune inhibitor for resectable dMMR tumors) might be an alternate method to consider in future trial design as well, especially for vulnerable populations in vulnerable times.

There are non—chemotherapy-based timing strategies that also could be evaluated, and in turn better incorporated into rational clinical trial design in addition to validated tissue-based and blood-based biomarkers. Validated assessments that could predict "aggressiveness" and growth curves of tumors would be a helpful tool in clinical decision-making, helping to determine which patients would not be harmed by delaying surgery during this pandemic, which patients would at least not be harmed by administering neoadjuvant chemotherapy until a safer time to perform surgery, and identifying those patients in whom the risk/benefit ratio tips toward benefit for not delaying surgery due to inherent risk of rapid tumor growth.

The current pandemic has forced us to reexamine these questions in new light of more practical and nonbiologic questions, most prominently in recent months the question of how to best ration PPE to preserve it for the most crucial, necessary, and most urgent of

medical cases. Many cancer-related surgeries are required as part of an intent-to-treat strategy; the challenge will be balancing the urgency with timing that would still serve the patient for best possible outcome, and still preserve the safety of health care workers. With the hanging possibility that the current wave of COVID-19 infections may not be the last in the months and years to come, this is a question that will recur and be necessary to address for the future as well as the immediate present. For this reason alone, we must think creatively and proactively to question and reassess rational strategies for standard-of-care treatment approaches and also for clinical trial design, taking all of these factors into account using available data.

Although such validated assessments may not exist currently, past studies may pave the way for such decision-making tools.[12] Such studies include biophysical and mathematical models of cancer cell behavior that identify patterns of tumor cell expansion, even occurring on the individual patient level.[13] At the convergence of mathematical oncology, cancer cell biology, and immunology, there may be a meeting point that will help solve modern and urgent problems in practical cancer treatment by informing better timing of cancer treatment.[14-16] An adaptive therapy strategy and clinical trial design, based on prediction models of the evolution of cancer cell growth and response to drugs, are already being used for clinical trials in metastatic castrate-resistant prostate cancer.[17] There is opportunity to leverage the evolution of the field of medical oncology as well to better incorporate perspectives from experts in mathematical oncology and bioengineering to likewise address this important aspect colon cancer biology into the way we design trials with therapeutic intent, with arms that reflect appropriate changes based on changes in tumors identified using serial liquid biopsies (e.g., circulating tumor DNA, pharmacogenomically profiled circulating tumor cells) and other biologic tools. The sequence and timing of treatment administration also should be closely reexamined, as the efficacy of treatment of MSI-H tumors in this immuno-oncology era may be enhanced by staggering timing with chemotherapy. For example, our recent preclinical studies showed that resecting tumor-draining lymph nodes in early-stage tumor significantly reduces antitumor immune response, and that sequential treatments with chemotherapies and immunotherapies improve tumor control.[18] This finding will require further extensive investigation but provides preliminary basis for additional investigation. Clinical implications may include making an argument against traditional upfront resection comprising primary tumor resection as well as of regional lymph nodes, and more so in favor of upfront chemotherapy as a precursor to "priming the pump" of innate immunity and thus establishing a long-term form of immune surveillance of cancer. In the current climate of potential risk of resection outweighing immediate benefit, at least for the foreseeable future, there is incidental opportunity to study this and other phenomena prospectively to confirm these findings in patients.

Although the COVID-19 pandemic has been thrust on the medical oncology community in short order, we can take the time to reflect on the best way to serve our current patients and manage their treatment safely, while also reflecting carefully on how we can serve them even more effectively in the future.

Disclosure

The authors have stated that they have no conflicts of interest.

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