



## Perspective

## The travails of therapeutic modifications in cancer care amidst the COVID-19 pandemic: Future directions and lessons learned



The coronavirus disease 2019 (COVID-19) pandemic continues to pose challenges of unparalleled magnitude. Unsurprisingly, COVID-19 amongst cancer patients has been associated with higher mortality rates and ventilation support, with the highest mortality associated with hematological malignancies [1–3]. The burgeoning risk of disease progression secondary to delayed treatment-seeking behavior precipitated by fears surrounding the pandemic has resulted in significant morbidity and mortality. While the risk stratification and categorization of cancer care priority remains elusive, we hereby provide some suggestions to bridge the chasm that exists in our current cancer care regimens despite recent suggestions pertaining to therapeutic modifications.

Cancer patients are at a relatively higher risk of contracting SARS-CoV-2 infection than the general population due to frequent exposure to ongoing immunosuppressive treatment [4]. Furthermore, patients with malignancies have demonstrated an increased tendency to develop severe respiratory dysfunction, consequently requiring prolonged intensive care stay compared to those without malignancy [4,5]. The ostensible reason for these observations is related to a history of chemotherapy or recent surgical intervention. Notably, patients undergoing chemotherapy or cancer treatment demonstrate a more rapid clinical decline than non-cancer patients. Based on the aforementioned predicaments, cancer care warrants urgent modifications in order to thwart the severe complications of COVID-19 in this vulnerable population.

Recently, a comment from Benoit You and colleagues from the French High Council for Public Health highlighted recommendations for adult patients with solid tumors in the context of COVID-19 [6]. We largely agree with their guidelines, and our comment further elucidates the unmet need for apt therapeutic modifications in cancer patients. We believe the chemotherapeutic regimens can be simplified in order to decrease the frequency of clinic visits as well as to decrease the risk of neutropenia. During this unprecedented crisis, tough decisions are warranted in a timely manner for the safety of our cancer patients, healthcare professionals, and the general public. Single agent capecitabine has been recommended in a previous study [5]. We further believe chronic, low-dose capecitabine as maintenance therapy can be employed with promising outcomes and a high level of safety in selected patients with gastrointestinal and breast cancers [7,8]. Similarly, capecitabine can replace intravenous fluorouracil (5-FU), especially infusion-related doses that require two visits for regimens containing oxaliplatin, irinotecan, and gemcitabine combinations [7,9]. A 21-day schedule can be instituted to decrease the frequency of visits rather than the current 28-day one. The bolus dosages of 5-FU can also be omitted at the least to further curb the risk of neutropenia.

Simplified biweekly schedules can be employed for combination regimens, including gemcitabine-cisplatin (s-GC), gemcitabine-

oxaliplatin (s-GemOx), gemcitabine-capecitabine (s-GemCap), and gemcitabine-nab-paclitaxel (s-GA) without compromising much therapeutic efficacy [10,11]. In addition, OPTI schedules, such as OPTIMOX and OPTINAB, can be selected during the COVID-19 crisis [12,13]. In patients at high risk of developing neutropenia, administration of growth factors should be considered [14,15]. Using the pharmacology of the chemotherapeutic and targeted agents, schedules can be modified. For example, bevacizumab can be modified to a three-week schedule at a dose of 7.5 mg/kg. Adjuvant therapy, except hormonal therapy, for certain tumor types can be delayed up to 12 weeks following curative-intent surgery to decrease hospital visits, thereby decreasing the risk of COVID infection. Home delivery services should be utilized for oral chemotherapies, supportive medications, and the flushing of porta catheters. Moreover, the administration of bisphosphonates such as alendronate and zoledronic acid should be delayed for now. Another extremely important aspect is related to palliative and hospice care during this pandemic. Telehealth has vitalized this pandemic by allowing health care professionals to interview their patients virtually. While nothing can replace a human touch in exacting times, patients report greater satisfaction with a video call compared to a phone call [16]. A proposed triaging strategy is delineated by Fig. 1 below and is adapted from the NICE guidance [17].

Cancer patients with prior likely exposure to SARS-CoV-2 who visited clinics for chemotherapy should be screened for COVID-19. Screening can be conducted using molecular or serological testing. The molecular method utilizes a reverse transcriptase polymerase chain reaction (RT-PCR) technique to diagnose current patients using a respiratory tract sample, such as a nasopharyngeal swab. This in turn guides isolation and treatment plans and helps separate infected cancer patients from the uninfected cancer patients awaiting chemotherapy. Serological testing involves the detection of antibodies against SARS-CoV-2 virus in patients with no or mild clinical symptoms. Enzyme-linked immunosorbent assay (ELISA) is performed on a blood sample to detect IgG or IgM antibodies using recombinant antigens derived from the SARS-CoV-2 spike protein. The samples are collected 14 to >21 days after symptoms first appear. The major benefit of serological testing is population surveillance to identify people with past infection who have recovered and developed immunity. These patients can also serve the purpose of plasma donation, which is demonstrating promising results.

Further, the categorization of cancer patients is instrumental in maintaining the delicate equilibrium between cancer care and requisite protection from COVID-19 infection. Oncological care amidst the pandemic is divided into 4 phases primarily based on the emergent nature and severity of the presenting symptoms. In some cases, for instance, chemotherapeutic regimens cannot be upended as doing so can portend debilitating outcomes. In these cases, high systemic

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chemotherapeutic doses are administered, and the resultant side effects often warrant consequent hospital visits. In such cases, we recommend that the patient history is sifted for prior therapeutic regimens and associated tolerance levels, and that a therapeutic dose believed to not elicit any adverse events is administered, even if sub-optimal [18]. We are cognizant that in some cases, compromising the chemotherapeutic dose, even to a minuscule extent, can yield greater mortality than COVID-19 itself does. We then suggest that the required therapeutic doses are administered but that prior to commencement, neutrophil counts are strictly monitored, and white cell growth factor is taken into consideration. Additionally, it is our position that steroids should not be used to manage the acute adverse events that result from chemotherapy, as steroids can further suppress the host immune system.

For various solid metastatic tumors, it is now a maxim that chemotherapy beyond the third cycle yields no additional benefits. Besieged by duress imposed by COVID-19, oncologists are now siding towards supportive treatments instead [19]. Additionally, oncologists expressed reduced preference towards systemic chemotherapy in the setting of breast cancer [20]. In line with this, primary surgery has become a preferred approach to triple negative and estrogen receptor (ER) negative breast cancers [20]. While we agree with these recommendations in the short-term, they might not be viable in the long run. For example, cancer cases not treated with adjuvant therapy initially might in turn require surgical intervention, which will indubitably expose cancer patients to infective ailments. We therefore vehemently champion the

notion that neoadjuvant therapies are employed to reduce the need for emergent surgical interventions and aid in preserving the health resources that are vulnerable to depletion sooner or later.

The need for modifying therapeutic cancer regimens is born through necessity and nurtured through an in-depth analysis of the debilitating consequences deprioritizing cancer care can foment. While efforts are being made to contain the proliferation of the COVID-19 pandemic, we should ensure that we are not headed towards another imminent pandemic—characterized, this time, by an exorbitant backlog of cancer patients requiring emergent care.

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**Author contributions**

TA, MHNG, ZIT: conceived the idea, designed the study, and drafted the manuscript.

TK, ME, UM, AHA: conducted literature search and created the illustrations.

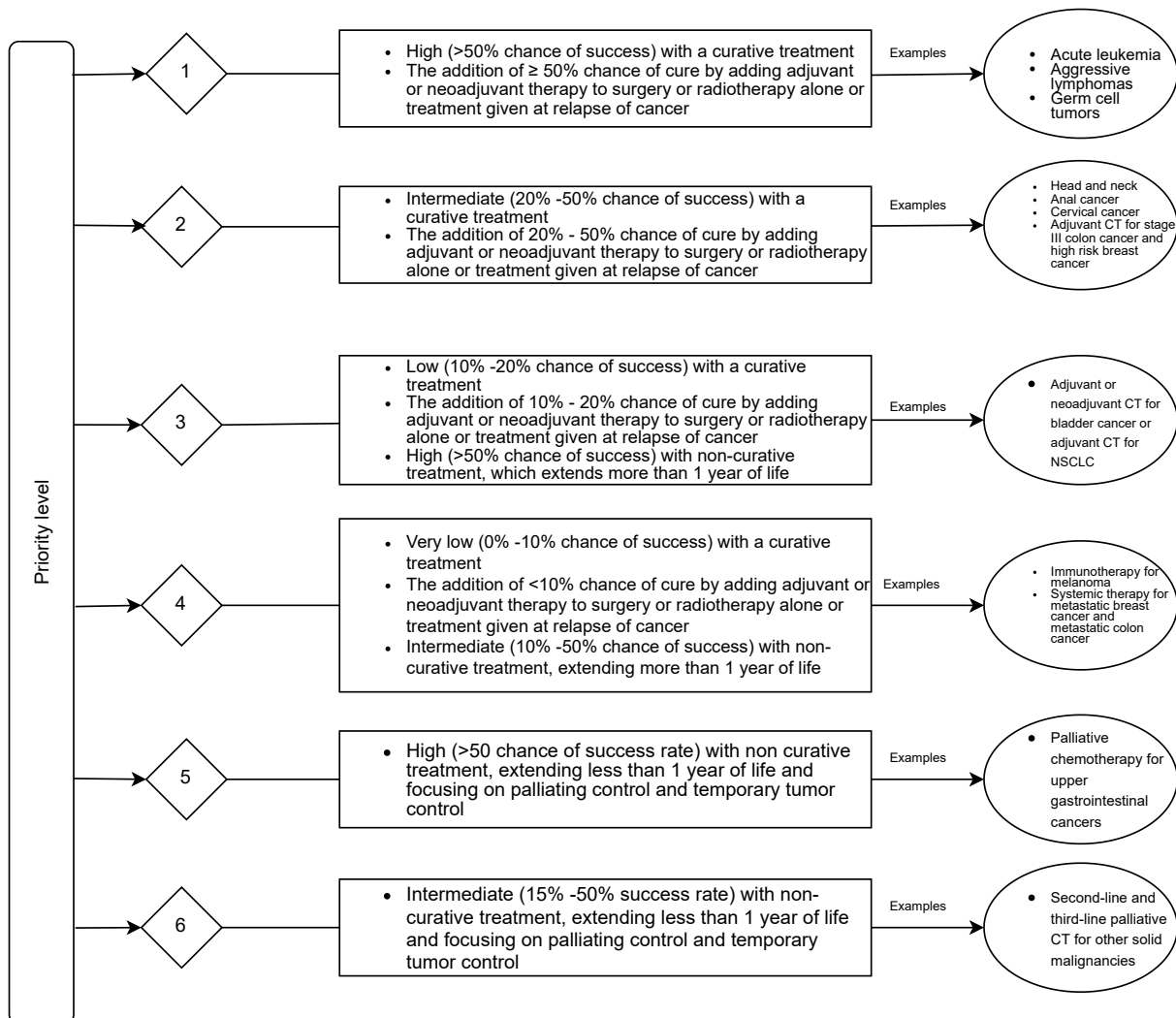


Fig. 1. A proposed triaging strategy based on the apt categorization of patients with regards to priority of care (adapted from the NICE guidance) [17].

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### Consent

NA.

### Declaration of competing interest

None.

### References

- [1] E. Dong, H. Du, L. Gardner, An interactive web-based dashboard to track COVID-19 in real time [published correction appears in *Lancet Infect Dis.* 2020 Sep;20(9): e215], *Lancet Infect. Dis.* 20 (5) (2020) 533–534, [https://doi.org/10.1016/S1473-3099\(20\)30120-1](https://doi.org/10.1016/S1473-3099(20)30120-1).
- [2] COVID Data Tracker, Centers for disease control and prevention, Retrieved 26 April 2021, from, <https://covid.cdc.gov/covid-data-tracker/#vaccinations>, 2021.
- [3] B.P. Venkatesulu, V.T. Chandrasekar, P. Girdhar, et al., A systematic review and meta-analysis of cancer patients affected by a novel coronavirus, *JNCI Cancer Spectr.* 5 (2) (2021), <https://doi.org/10.1093/jncics/pkaa102> pkaa102. Published 2021 Feb 24.
- [4] W. Liang, W. Guan, R. Chen, et al., Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China, *Lancet Oncol.* 21 (3) (2020) 335–337, [https://doi.org/10.1016/S1470-2045\(20\)30096-6](https://doi.org/10.1016/S1470-2045(20)30096-6).
- [5] L. Sun, Y. Xu, T. Zhang, Y. Yang, Impact of the COVID-19 outbreak on adjuvant chemotherapy for patients with stage II or III colon cancer: experiences from a multicentre clinical trial in China, *Curr. Oncol.* 27 (3) (2020) 159–162, <https://doi.org/10.3747/co.27.6529>.
- [6] B. You, A. Ravnaud, A. Canivet, et al., The official French guidelines to protect patients with cancer against SARS-CoV-2 infection, *Lancet Oncol.* 20 (2020) 30204–30207, [https://doi.org/10.1016/S1470-2045\(20\)30204-7](https://doi.org/10.1016/S1470-2045(20)30204-7), pii: S1470-2045, ([Epub ahead of print]).
- [7] J.F. Sun, R.R. Wu, C. Norris, et al., Safety of chronic low-dose capecitabine as maintenance therapy in gastrointestinal cancers, *Gastrointest Cancer Res* 3 (2009) 134–140.
- [8] P. Fedele, A. Marino, L. Orlando, et al., Efficacy and safety of low-dose metronomic chemotherapy with capecitabine in heavily pretreated patients with metastatic breast cancer, *Eur. J. Canc.* 48 (1) (2012) 24–29, <https://doi.org/10.1016/j.ejca.2011.06.040>.
- [9] R. Vidra, R. Bodea, V. Mercea, A. Nemes, Challenges of pancreatic cancer chemotherapy in the COVID-19 era, *Jun 4, J. Gastrointest. Liver Dis.* 29 (2) (2020) 273–275, <https://doi.org/10.15403/jgld-2527>. PMID: 32531001.
- [10] M.W. Saif, Y. Suarez, D.W. Hackenjos, et al., Simplified/same day (s)-GOLF as first-line treatment of metastatic carcinoma of unknown primary (CUP), *J. Clin. Oncol.* 34 (15 suppl) (2016), e15665.
- [11] J. Li, M. Merl, M.X. Lee, K. Kaley, M.W. Saif, Safety and efficacy of single-day GemOx regimen in patients with pancreaticobiliary cancer: a single institution experience, *Expert Opin. Drug Saf.* 9 (2010) 207–213.
- [12] V. Relias, A. Maloney, M.H. Smith, M.W. Saif, Does "OPTINAB" strategy ("stop-and-go") work in treatment of advanced pancreatic cancer (APC) with nab-paclitaxel-gemcitabine? *Canc. Chemother. Pharmacol.* 80 (2017) 371–375.
- [13] M.W. Saif, Does OPTIMOX strategy ("stop-and-go" approach) also work in treatment of pancreatic cancer with oxaliplatin-based regimens? *JOP* 9 (2008) 658–663.
- [14] N. Hakim, J. Chi, H. Rehman, et al., First analysis of same-day pegfilgrastim use with concurrent capecitabine-based regimens in pts with GI malignancies, *J. Clin. Oncol.* 38 (4 suppl) (2020) 817, 817.
- [15] R.M. Matera, V. Relias, M.W. Saif, Safety and efficacy of same-day administration of pegfilgrastim in patients (pts) receiving chemotherapy for gastrointestinal (GI) malignancies, *J. Clin. Oncol.* 35 (15 suppl) (2017) 10112, 10112.
- [16] H.L. Li, Y.C. Chan, J.X. Huang, S.W. Cheng, Pilot study using telemedicine video consultation for vascular patients' care during the COVID-19 period, *Ann. Vasc. Surg.* 68 (2020) 76–82, <https://doi.org/10.1016/j.avsg.2020.06.023>.
- [17] Tools and Resources COVID-19 Rapid Guideline: Delivery of Systemic Anticancer Treatments, NICE Guideline [NG161], 2021, <https://www.nice.org.uk/guidance/ng161/resources/>.
- [18] P. Fedele, V. Sanna, A. Fancellu, A. Marino, N. Calvani, S. Cinieri, De-escalating cancer treatments during COVID 19 pandemic: is metronomic chemotherapy a reasonable option? *Crit. Rev. Oncol. Hematol.* 157 (2021) 103148, <https://doi.org/10.1016/j.critrevonc.2020.103148>.
- [19] H.O. Al-Shamsi, W. Alhazzani, A. Alhurajji, et al., A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group, *Oncol.* 25 (6) (2020) e936–e945, <https://doi.org/10.1634/theoncologist.2020-0213>.
- [20] M.L. Gasparri, O.D. Gentilini, D. Lueftner, T. Kuehn, O. Kaidar-Person, P. Poortmans, Changes in breast cancer management during the corona virus disease 19 pandemic: an international survey of the European breast cancer research association of surgical trialists (EUBREAST), *Breast* 52 (2020) 110–115, <https://doi.org/10.1016/j.breast.2020.05.006>.

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